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OBSERVATIONS ON THE DESCENT OF THE TESTICLE WITH SPECIAL REFERENCE TO SPONTANEOUS DESCENT AT PUBERTY

BY

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The testicle is normally in the scrotum at birth, but its descent may be arrested at any point from its origin near the kidney to its final destination. The majority of so-called undescended testicles should be described as partially descended testicles. At the present time, surgery and endocrine therapy are active lines of treatment. However, there is an increasing tendency to trust to spontaneous descent at puberty, and the object of this paper is to justify that policy in particular cases.

Previous reports of spontaneous descent

In 1918, H. G. Armstrong, Medical Officer to Wellington College, Berkshire, wrote in the *Guy's Hospital Gazette* that during the previous seven years, seven boys among approximately one thousand new entrants were found to have complete absence of both testicles from the scrotum. All seven had small genitalia ; the scrotum resembled a small piece of wrinkled skin ; pubic hairs were absent. Four had rarefaction of the outer third of the eyebrows and one was of a Mongolian type. Three suffered from nocturnal enuresis. All were given half a grain of thyroid extract twice daily over a considerable period. In six the testicles descended, but in the seventh the left testicle entered the scrotum, the right the perineum. By the end of adolescence the testes and genitalia grew to normal size, although some of the boys had only scanty pubic hair. He never had the same success with a single undescended testicle. Whether or not the thyroid was responsible or whether or not the descent would have occurred spontaneously at puberty cannot be definitely decided, but the subsequent evidence will point to the probability of spontaneous descent.

Although Bjerre only published his figures in 1937, his researches on 251 cryptorchids date back to 1900. Of these 196 were operated on between 1900–1930 and the testicle fixed in the scrotum. Many had passed puberty, but the average age at operation was twelve. The results were good in fifty-eight, bad in thirty-two and followed by atrophy in ten per cent. The further the testicle had descended in its course from the abdomen, the better were the results. A six months' interval was allowed to elapse between the operations for bilateral non-descent. For a large series dating from 1900 these figures compare not unfavourably with the successes of other surgeons. Bjerre compared these

196 cases with a control series of 188 boys composed of the fifty-five unoperated cases added to 133 boys in a school where the medical authorities disapproved of operation. One hundred and nineteen (sixty-three per cent.) of these descended spontaneously and the school statistics showed that descent nearly always occurred about the age of fifteen. In the other group accurate information was not available.

Drake has reported spontaneous descent in twenty-four of thirty-eight cases at ages ranging from ten to sixteen.

Williams observed 2,104 boys, in whom spontaneous descent occurred in twenty-four (sixty-three per cent.) of thirty-eight unilaterally undescended testicles, and in fourteen (sixty-seven per cent.) of twenty-one bilaterally undescended testicles. Ten boys were not seen for a sufficient time for adequate observation, and six boys had a hernial sac or a previous operation for one. Omitting these boys, Williams found that descent took place in twenty-four of the twenty-seven unilateral (eighty-nine per cent.), and in fourteen of the sixteen bilateral, (eighty-seven per cent.), and that the age of descent was as follows :

AGE OF DESCENT		UNILATERAL	BILATERAL
11-12 years 2	2
12-13 " 5	3
13-14 " 4	1
14-15 " 7	5
15-16 " 5	3
16-17 " 1	1

Treatment with gonadotrophic hormones

Bigler, Hardy and Scott (1938a) have recently summarized eighteen reports of the hormonal treatment of undescended testicles. The dosage varied considerably, e.g. in Spence and Scowen's series (1935), 500 rat units were given intramuscularly routinely twice a week for an average of four months, but the limits were two weeks and fourteen and a half months. The preparations used by the eighteen were extract of anterior lobe of hypophysis, either obtained directly or from the urine of pregnant women, and follutein, or a combination of these. Proprietary names of the preparations are often used. Of the 267 undescended testicles treated, 176 (sixty-five per cent.) completely descended.

Spence and Scowen (1938) have brought their experiences up to date. They find all retractile testes will respond to hormone therapy, that in their series of seventeen bilaterally and eleven unilaterally undescended testicles situated in the inguinal canal which could not be manipulated into the scrotum, seventy-six per cent. of the bilateral and sixty-four per cent. of the unilateral group responded to hormone therapy, whereas a successful result was not likely to occur if the testicle were not palpable.

Bigler and his fellow workers (1938b) in an investigation designed to test the value of hormone therapy were unable to get such high percentages of successes, even in cases in which they were satisfied that the dosage was adequate. Of thirty-one undescended testicles in twenty-three patients treated with antuitrin-S, fourteen (forty-five per cent.) remained undescended ; one failed to remain descended : of forty undescended testes in thirty-two patients treated with gonadotrophic hormone obtained from the urine of pregnant women, ten (twenty-five per cent.) completely descended into the scrotum, but only seven remained there : and of twenty undescended testicles in sixteen patients treated with a mixture of both, eight (forty per cent.) showed complete descent but only five (twenty-five per cent.) remained descended. They believe that if a testicle is going to descend, it will do so before 4,000 rat units have been given.

Results of surgical treatment

Bigler and his co-workers (1938a) have also reviewed the surgical aspect. They found from a study of the literature up to 1922 that operation was a failure in fifty per cent. of cases ; that American surgeons reported 'cures' ranging from forty-two to ninety-two per cent. In America two operations are in vogue : the Bevan operation, probably the more popular, consists of mobilizing the testicle and after elongation of the cord suturing the testicle to the lowest part of the scrotum, and Torek's operation, which is becoming more popular and consists of freeing the testicle and suturing it to the fascia of the upper part of the thigh ; after three to six months the testes and scrotum are dissected from the thigh.

In England a third type of operation is often performed. This consists of anchoring the freed testicle in the scrotum by pushing it through a hole made in the scrotal septum. Turner, who usually practises this method, sums up his experience of fifty patients as follows :

COMPLETE SUCCESS	Testicle hangs normally and easily and is well in scrotum	35, i.e., 70 per cent.
SOME ABNORMALITY	8, i.e., 16 per cent.
FAILURES	7, i.e., 14 per cent.

Object of present investigation

It will be agreed that each of the three methods of treatment has a creditably high percentage of cures. My interest in this problem started in 1930, when I was appointed medical officer to two schools, one with approximately six hundred boys from thirteen to eighteen years of age, and one of four hundred from nine to eighteen years. Schapiro published his findings in September, 1930, but I was not aware of them until 1935, when Spence and Scowen published their paper, and my object was to study the natural history of the late descent as a biological problem, especially to determine if operation was always necessary, as was generally taught and practised in my own medical school. Other interesting facts arose from my observations, as detailed notes below show.

Case 1. UNDESCENDED TESTICLES. PLURIGLANDULAR DYSTROPHY. DESCENT WHEN AGED 16 AFTER TAKING TESTICULAR EXTRACT.

In 1929, a stunted boy of thirteen years and nine months on admission to school weighed 102 lb. and was 55 inches high, compared with normal of 96 lb. and 61 inches. In May, 1932, he weighed 124 lb. and was 59 inches high. His facial expression was that of an adult, but his mental attitude was that of a child some years younger than his age. From 1929-1932 he took half a grain of extract of dry thyroid and two grains of extract of whole pituitary gland. These were omitted in May, 1932, and by November, 1932, he had grown two and a half inches and put on only nine pounds ; his mental capacity had increased. The chief concern of his parents was the failure of the testicles to descend. In March, 1932, he was given forty minims Orchitogene (Maroglian) night and morning and by June of that year his testicles became fully descended and remained so, although he took no more of this preparation. This boy was referred by my predecessor Dr. A. I. Simey to Sir Walter Langdon Brown, who prescribed the various endocrine preparations for him, and his help is gratefully acknowledged. Whether or not the descent was 'post' or 'propter' the orchitogene, it is not possible to say.

Case 2. BILATERAL UNDESCENDED TESTICLES. SPONTANEOUS DESCENT, RIGHT AT 13 YEARS, LEFT AT 13 YEARS 10 MONTHS. NORMAL DEVELOPMENT. OPERATION FOR LEFT INGUINAL HERNIA AT AGE 2 YEARS.

A boy born in December, 1921, was first seen by me in May, 1933. Both testicles were undescended. In July, 1934, the right testicle could be made to descend, but not the left. In May, 1935, both testicles were in scrotum. He was then aged thirteen years and ten months. In December, 1935, both testicles were still in the scrotum. The penis was still small, and the boy fat, especially his abdomen and breasts. In June, 1936, the testicles were the size of marbles, and in June, 1937, were of normal size. Puberty was by then well advanced. At the age of two years he had an operation for a left inguinal hernia, which apparently was completely successful. He had been seen in September, 1929, at the age of eight, by Dr. Simey, who had also noted that both testicles were undescended.

Case 3. BILATERAL UNDESCENDED TESTICLES. GENERALIZED OBESITY, RIGHT TESTICLE BROUGHT INTO SCROTUM AND FIXED BY TRANSPLANTATION THROUGH THE SEPTUM. DESCENT OF LEFT TESTICLE SPONTANEOUSLY AT AGE 13½ YEARS.

This boy was first seen in October, 1935, when he was eleven years and three months of age. His height was 59½ inches, weight 96½ lb. The obesity was generalized. Both testicles were situated in the mid-inguinal region. In May, 1936, the right testicle was palpable above the external inguinal ring; the left was not palpable. In December, 1936, the right testicle was operated on; it was easily brought down into the scrotum and was put through a hole in the septum into the contra-lateral half of the scrotum. When the boy was seen in June, 1937, the testicle was of apparently normal size. No change was noted in January, 1938. In March, 1938, the boy noticed that the left testicle had fully descended and both are of equal and of good size in the left half of the scrotum. In October, 1938, puberty was just starting.

Case 4. BILATERAL UNDESCENDED TESTICLES. GENERALIZED OBESITY. SPONTANEOUS DESCENT AT AGE 13½ YEARS.

A boy aged thirteen and a half entered school in September, 1936. His weight was 116 lb. (average 93½), height 58½ inches (normal 60). Obesity was generalized. Neither testicle had descended. The scrotum was flat against the perineum. By December, 1936, both testicles had descended; the boy himself had noted this. In February, 1937, I was able to palpate both testicles in the scrotum, which was considerably flattened. His weight was 113½ lb. and his height 59 inches. In October, 1938, both testicles were in the scrotum, which had become a pouch. The pubic hair was scanty.

Case 5. BILATERAL UNDESCENDED TESTICLES. INFANTILE SCROTUM. SPONTANEOUS DESCENT AT 13½ YEARS.

This boy was first seen in October, 1933, aged eight years and four months. His height was 52½ inches, weight 62½ lb. In June, 1936, at the age of eleven, both testicles were undescended. In December, 1936, the scrotum was not yet a bag, and neither testicle was palpable. In June, 1937, at the age of twelve, both testicles were in the scrotum, and were of good size; the penis was growing, and the scrotum was a definite bag. The boy's height was 59 inches and he weighed 80 lb. In October, 1938, the testicles had developed, although pubic hair was still very scanty.

Case 6. BILATERAL UNDESCENDED TESTICLES. DESCENT AT PUBERTY.

This boy was first seen in November, 1935, aged twelve and a half years. His height was $58\frac{1}{4}$ inches, weight $94\frac{1}{2}$ lb. There was no abnormality except that neither testicle was in the scrotum. He had never noticed them. Pubic hairs were just appearing. In June, 1936, pubic hairs were half an inch long; both testicles were in the scrotum, and were the size of lentils. In December, 1936, both testicles were well in the scrotum and many pubic hairs were present. In June, 1937, both testicles were as large as nutmegs, and pubic hairs numerous. The penis was of normal size. The boy was then $61\frac{1}{2}$ inches tall and weighed 109 lb. He was seen again in October, 1938, when both testicles had grown to normal size.

Case 7. BILATERAL UNDESCENDED TESTICLES. RIGHT DESCENDED AT $14\frac{1}{2}$ YEARS. LEFT DESCENDED AT 15 YEARS.

The patient was born in February, 1923; when first examined in November, 1935, his height was $56\frac{1}{4}$ inches and weight $76\frac{1}{2}$ lb.; neither testicle could be felt in the scrotum or inguinal canal. When re-examined in June, 1936, and again in December, 1936, testicles were not palpable and puberty had not started. In June, 1937, the right testicle was in the scrotum and the left just outside external inguinal ring. Testicular sensation was normal. Puberty had not started. In January, 1938, both testicles had completely descended, and puberty was starting. In October, 1938, both testicles were equal and of good size, and puberty well advanced.

Case 8. BILATERAL UNDESCENDED TESTICLES. BOTH IN INGUINAL CANAL. PUBERTY ADVANCED. PATIENT $15\frac{1}{2}$ YEARS.

Born in May, 1922, the patient was first seen in February, 1935. Both testicles were then high up in the inguinal canal. In June, 1935, there was no change; testicular sensation was normal. When examined in December, 1935, and June, 1936, both testicles were half-way down the inguinal canal; pubic hairs were plentiful. In June, 1937, both testicles were situated at the upper end of the inguinal canal and puberty was advancing. Examination in January and October, 1938, showed no change. Sensation in both testicles was normal. The patient's present height is $61\frac{1}{8}$ inches and weight 78 lb.

Case 9. BILATERAL UNDESCENDED TESTICLES. DESCENT OF LEFT AT AGE $11\frac{1}{4}$ YEARS. RIGHT STILL UNDESCENDED AGE $12\frac{1}{4}$ YEARS.

Patient was born in February, 1924, and was first seen in January, 1935. His height was then $56\frac{1}{2}$ inches and weight $75\frac{1}{2}$ lb. Both testicles were half-way down the inguinal canal. In July, 1935, the left testicle was in the scrotum, and the right in the inguinal canal. A few pubic hairs were present. In December, 1935, there was no change. In June, 1936, sparse pubic hairs had appeared. The right testicle was still half-way down the inguinal canal. (He has now left the neighbourhood, and further follow-up is impossible.)

Case 10. UNDESCENDED RIGHT TESTICLE. SPONTANEOUS DESCENT AT AGE OF 14 YEARS. LATE PUBERTY.

A boy aged thirteen and a half, a scholar of average build, entered school in September, 1934. The right testicle was half-way down the inguinal canal and had normal sensation. The blood pressure was 95/65. On November 21st, 1934, there was no change, but on December 18th, 1934, the testicle had descended completely into the scrotum and was as large as its fellow. Puberty had not started. In February, 1935, the condition was as before. In May, 1935, the boy was fourteen; the testicle was now completely in the scrotum.

Case 11. RIGHT UNDESCENDED TESTICLE. STILL UNDESCENDED ALTHOUGH PUBERTY IS ADVANCED AND PATIENT IS 17 YEARS.

Patient was born in September, 1921. In July, 1935, the left testicle was found to be the size of a bantam's egg and in the scrotum ; the right was small and in the inguinal canal. The boy's intelligence was normal. In December, 1935, there was little change ; puberty was starting. In June, 1936, the right testicle was the size of a kidney bean and at the external inguinal ring. Sensation was normal, and puberty was well advanced. In December, 1936, there was no change, and puberty was far advanced. In June, 1937, the right testicle was still in the inguinal canal. Re-examined in December, 1937, and October, 1938, there was no change ; the testicle was still the size of a kidney bean and palpable at the external inguinal ring.

Case 12. RIGHT UNDESCENDED TESTICLE — OPERATION. ATROPHIC TESTICLE REMOVED.

A boy entered school in May, 1931, aged thirteen years nine months. The right testicle was still in the inguinal canal and would not descend. Puberty had not started. His weight was 98 lb. and height 63 inches. Operation was advised to try to get the testicle to come down into the scrotum, and though the father was opposed to this, he had it performed in September, 1932, by Mr. Frank Barnes. At operation, the testicle was found to be so atrophic that the only course was total removal. This made no difference to the boy's physical development, and he later won a scholarship at Oxford.

Case 13. UNDESCENDED LEFT TESTICLE. PUBERTY ADVANCED. TESTICLE IMPALPABLE AT AGE OF 13½ YEARS.

Born in 1925, the boy was seen in October, 1933, when his weight was 55½ lb. and height 51½ inches, and in June, 1936 his weight was 73 lb. and height 56½ inches. The left testicle was undescended. In December, 1936, the left testicle was impalpable. Pubic hair was appearing. In June, 1937, the condition of the left testicle was unchanged. The penis was large, and the right testicle the size of a pigeon's egg. In October, 1938, the left testicle was still not palpable, although puberty was far advanced.

Case 14. UNDESCENDED RIGHT TESTICLE. ENLARGEMENT BUT NOT DESCENT WITH PREGNYL. OPERATION ON ECTOPIC TESTICLE, WHICH WAS FIXED IN SCROTUM.

This boy entered school in September, 1933, at the age of thirteen years and eight months. His right testicle was undescended and puberty was advanced. In May, 1936, when the boy was sixteen, it was decided to try to get the testicle to descend with pregnyl. He was given two courses of twelve injections with 500 rat units from May to September, 1936, and a further twelve injections from October to December, 1936. This had the effect of causing the testicle to enlarge considerably. He was given a further course from January to March, 1937, and although the testicle, which was originally no bigger than a pea, had increased to more than twice this size, it would not come down any further than just below the internal inguinal ring. He had been seen in consultation with Sir Walter Langdon Brown on two occasions, and on the third occasion, in April, 1937, it was decided that the testicle was probably mechanically prevented from descending and operation was advised. This was performed by Mr. W. D. Doherty on May 1, 1937. The testicle was found to be of considerably larger size than was expected from manual palpation and to have ridden over the anterior border of the internal inguinal ring.

With considerable difficulty the testicle was brought down into the scrotum and fixed there by transposition through the septum. Six weeks later, it was still in position, and was rapidly approaching the size of its fellow. He has been given one more course of pregnyl injections with beneficial results.

Case 15. UNDESCENDED TESTICLE. PUBERTY ADVANCED. ATTEMPT TO MAKE TESTICLE DESCEND WITH PREGNYL. SUCCESSFUL OPERATION.

A boy entered school in January, 1937, aged thirteen and a half years. His height was $64\frac{1}{2}$ inches (average 60 inches), and his weight 134 lb. (average $93\frac{1}{2}$ lb.). The right testicle was found at the upper end of the inguinal canal. Puberty was advanced. He was over weight, even allowing for his height. He was given a course of twelve injections of pregnyl, at bi-weekly intervals, of 500 rat units. On March 10, the testicle was half-way down the inguinal canal. Between February and December, 1937, he had four courses of twelve injections of pregnyl (500 units bi-weekly) with approximately a month's rest between each course. The testicle did not descend, but steadily increased in size. In December, 1937, he was operated on by Mr. L. R. Braithwaite, who wrote : 'The condition of the testis was one of ascent and not the usual kind of undescended. The testis had left the external ring, as you described, and had turned completely upwards, so that the lower pole was pointing towards the right shoulder. It was, therefore, a very easy matter to turn it down and get it into the upper part of the scrotum, and this was done without any division of anything else. I am quite sure, though it may be rather high in the scrotum for a while, that it will descend perfectly well.'

He was given one more course of twelve injections of pregnyl and the testicle fully descended and was equal to its fellow.

Case 16. RIGHT UNDESCENDED TESTICLE. SPONTANEOUS DESCENT.

A boy, when aged eleven, in 1932 was under observation at Alton by Sir Henry Gauvain, who noticed that the right testicle was undescended and could not be felt in the inguinal canal. In September, 1935, when he entered school, and on two subsequent occasions, his testicle was found to be in the scrotum. On entry he was 16 lb. and $1\frac{1}{4}$ inches under average weight and height.

Case 17. UNDESCENDED LEFT TESTICLE. DESCENT AT AGE 14 YEARS, 8 MONTHS BEFORE PUBERTY. LATE ERUPTION OF TEETH.

A boy aged thirteen years eight months entered school in September, 1935. The left testicle could be pushed down as far as the external ring. Sensation was normal. He was examined at intervals, but no change occurred until September, 1936, when the testicle descended fully into the scrotum. There was no sign of puberty. All his teeth were late in erupting, especially his canines, which erupted in his fifteenth year, i.e. two years later than normal. The association of the late eruption of the canines and the late descent of the testicles has been noted by Marvin. I have looked for this carefully in all my cases of undescended testicles, but this is the only one in which I have seen the connexion.

Case 18. SPONTANEOUS DESCENT OF TESTICLE AT AGE $13\frac{1}{2}$ YEARS.

A boy came with a note from his doctor to say he had an undescended testicle, which was going to be operated on before entering school. However, during the holidays it started to descend and by the beginning of term, when he was thirteen years and nine months, it was normally in the scrotum. Puberty was in progress.

Case 19. UNDESCENDED RIGHT TESTICLE. DESCENT AT AGE OF 13½ YEARS. TESTICLE SMALLER THAN ITS FELLOW. CAUSE OF DELAYED DESCENT POSSIBLY MECHANICAL.

Born in March, 1920, the boy was first seen in May, 1933. His height was 58½ inches, and weight was 82 lb. The right testicle, which appeared normal in size, was lying at the lower end of the inguinal canal, but could be pushed just into the scrotum. In June, 1933, while in camp, he stretched out vigorously. This gave him acute pain in the inguinal region, and he noticed after this that his testicle had come down. I saw him again in November, 1933. Puberty was just starting. The right testicle was half the size of its fellow. In February, 1935, there was no change. Sensation was normal. In December, 1935, pubic hair was abundant. The right testicle was two-thirds the size of the left, but both were large. He left school in 1936. It is difficult to explain the exact sequence of events. It is possible that the testicle was prevented mechanically from entering the scrotum, perhaps by an adhesion in the inguinal canal, too small an external inguinal ring, or that the testicle was anterior to the canal. The sudden movement might have overcome any one of these three factors. Another interesting feature is the development of the testicle after it descended.

Case 20. UNDESCENDED LEFT TESTICLE. DESCENT AS FAR AS INGUINAL CANAL. PUBERTY ADVANCED AT AGE OF 13½ YEARS.

Born in December, 1923, the boy was seen in September, 1932, November, 1933, and July, 1935. The left testicle was undescended. There was steady increase in height and weight from 54½ inches and 67½ lb. to 64½ inches and 114 lb. in June, 1937. In November, 1933, he had tonsillar glands removed for a mild tuberculous infection. His intelligence was well up to the average. In December, 1935, there was no change in the testicle, and in June, 1936, the left testicle was still impalpable. In December, 1936, the left testicle was felt at the top of the inguinal canal and was the size of a pea. Puberty was advancing. In June, 1937, puberty was well advanced; left testicle was still at the top of the inguinal canal. The patient has left the district, and further observation has not been possible.

Case 21. RIGHT UNDESCENDED TESTICLE AND INGUINAL HERNIA. OPERATION AGED 3 YEARS. CURE OF HERNIA. TESTICLE HALF THE SIZE OF ITS FELLOW AND IN INGUINAL CANAL.

A boy born November 15, 1923, was operated on when aged three years for a right inguinal hernia and undescended testicle. The operation for hernia was successful, but when examined in September, 1935, the right testicle, which was half the size of the left, was still in the inguinal canal. His height then was 55½ inches, and his weight 69 lb. He has been seen in June, 1936, December, 1936, and June, 1937. His physical condition was the same and there were no signs of puberty. In October, 1938, the testicle was at the lower end of the inguinal canal, was freely movable, and half the size of its fellow.

Case 22. RIGHT INGUINAL HERNIA AND UNDESCENDED TESTIS WHICH REMAINS AT EXTERNAL INGUINAL RING AT AGE OF 14½ YEARS.

Born in March, 1923, the boy was first seen in October, 1934. His height was 58 inches, and weight 76 lb., which had increased to 62½ inches and 100 lb. in June, 1937. In October, 1934, aged eleven and a half years, the right testicle was half way down inguinal canal. In December, 1935, and on each re-examina-

tion up to June, 1937 (at age of fourteen and a half) the right testicle was at the external inguinal ring and no pubic hairs were present. He had a large right inguinal hernia which was constantly present in the inguinal canal. In October, 1938, the hernia was still present and the testicle could be felt with difficulty inside it.

Case 23. RIGHT UNDESCENDED TESTICLE AND INGUINAL HERNIA. PUBERTY ADVANCED. OPERATION FOR HERNIA. TESTICLE REMAINS AT EXTERNAL INGUINAL RING.

A boy born in October, 1922, was first seen in March, 1934. His height was then 57½ inches and weight 79½ lb., increasing to 66 inches and 127 lb. in June, 1937. His intelligence was just below the average. In March, 1934, a right inguinal hernia was present. This was easily reduced. The right testicle did not descend. Puberty was starting. In June, 1936, he had recently had an operation for right inguinal hernia. The testicle was then at the external inguinal ring, was the size of a pea, and half the size of its fellow. (Throughout this paper sizes are compared by the apparent length of the testicle from pole to pole and width from side to side. A testicle the axes of which are twice that of its fellow is approximately eight times its volume.) In December, 1936, there was no change, but puberty was far advanced. In June, 1937, there was no change. He has now left school, and further observations are unobtainable.

Case 24. UNDESCENDED RIGHT TESTICLE. UNSUCCESSFUL OPERATION AT AGE OF 9 YEARS. FAILURE TO INDUCE DESCENT WITH PREGNYL.

A boy had an operation on his right testicle in 1932, when he was aged nine years. The attempt to bring down the testicle was unsuccessful. He was first seen in May, 1936. His mother was anxious to do everything she could for the boy, and agreed that he should have a course of injections of pregnyl. He was given five hundred rat units twice a week, commencing in June, 1936, and was given twenty-four injections in June, July, and August. At first there was a slight response, in that the testicle enlarged slightly to the size of a small pea ; but despite the fact that he was given two further courses of twelve injections of the same strength, the testicle failed to enlarge further or to descend, and in May, 1937, it was decided that it was no longer feasible to continue the injections.

Discussion

An analysis of these twenty-four cases will show that there are coincident factors associated with the original failure to descend, which give a clue to the ultimate prognosis.

Age incidence of undescended testicle.—In a school, the constant addition to and subtraction from its members makes it almost impossible to work out accurately the age-incidence. The table below is given with the knowledge that the experimental error is bound to be large ; but nevertheless it is significant that none of the 418 boys from sixteen to twenty had an undescended testicle. Case 14 was operated on on May 1, 1937. It is true there was none between eight and twelve, but this group only numbers 55. The majority are in the age-group of twelve to sixteen.

As those with an associated hernia or previous operation for a hernia have a completely different prognosis, it is wise to consider the group without hernia separately, and this is shown in the last column. The same criticism about the groups over fifteen and under twelve still holds good.

AGE IN YEARS	NUMBER IN BOTH SCHOOLS ON JUNE 1, 1937	BOYS WHO HAD UNDESCENDED TESTICLES WHEN FIRST OBSERVED (CASE NO. IN SERIES)	BOYS WITH UNDESCENDED TESTICLES ON JUNE 1, 1937			BOYS WITH UN- DESCENDED TESTICLES WITHOUT ASSOCIATED HERNIA ON JUNE 1, 1937	
			NO.	CASE NO. IN SERIES	PERCENTAGE IN AGE GROUP	NO.	PERCENTAGE IN AGE GROUP
19-20	2	—	—	—	—	—	—
18	63	—	—	—	—	—	—
17	157	14	—	—	—	—	—
16	196	10	—	—	—	—	—
15	185	2, 7, 8, 11, 16, 17, 24	4	7, 8, 11, 24	2·2	3	1·6
14	187	4, 6, 15, 22, 23	3	15, 22, 23	1·6	1	0·5
13	76	3, 20, 21	3	3, 20, 21	4·0	1	1·3
12	63	5, 13	1	13	1·6	1	1·6
11	31	—	—	—	—	—	—
10	12	—	—	—	—	—	—
9	10	—	—	—	—	—	—
8-9	2	—	—	—	—	—	—
Total	984		11		1·1	6	0·6

Cases No. 1, 9, 12, 18 and 19 had left school by June 1, 1937.

Associated conditions. OBESITY.—The first case is obviously an exception, and is quite different from the next three cases. His obesity was limited to the trunk ; fat was noticeably absent from his face. Cases 2, 3, 4 had generalized obesity and small genitalia, and the testicle had not descended on either side when first seen ; but descent was complete in all cases at approximately the onset of puberty. In my opinion the right testicle in Case 3 would have descended spontaneously. If this contention is admitted, then the operation was doubly disadvantageous, because the testicle was misplaced.

BILATERAL NON-DESCENT.—In addition to the first four cases, Cases 5 to 9 were affected bilaterally on the first examination ; in cases 5, 6, 7 descent at approximately puberty was spontaneous. In case 9 the left testicle descended when the patient was eleven years and three months, but the right was undescended at twelve and a half years, when puberty (which throughout this paper is judged by the appearance of pubic hairs) was starting. Unfortunately further follow-up has been impossible. The testicles of case 8 have failed to descend at sixteen and a half years and operation is being considered by his parents on the advice of his general practitioner. The remaining cases were unilateral, affecting the right in eleven instances, the left in three, and in one no note was made.

ANATOMICAL FACTORS, PARTICULARLY THE PRESENCE OF COINCIDENT HERNIA.—Cases 10 to 20 had no hernia, cases 2, 21, 22, 23, 24 each had a hernia on the same side as the undescended testicle. Descent took place spontaneously in cases 10, 16, 17, 18, 19, and after hormone therapy and operation

in cases 14 and 15 and not in cases 11, 12, 13 or 20. These have had neither hormone therapy nor operation. In the second group, descent has taken place only in case 2. A most interesting feature is the development of the hernia in case 22 at the age of puberty and the presence of the testicle in it, especially as recently Browne (1938) has stated on good evidence that 'a testicle that is in the inguinal canal cannot be felt through the skin.' In this case the testicle was thought to be in the inguinal canal before and after the appearance of the hernia. Spence (1938) has stated that in six of his patients who were subsequently operated on after unsuccessful hormone therapy, the testes which had been palpable through the skin prior to operation were found at operation to be lying in the inguinal canal. In fact, the operative finding in four of these six showed anatomical peculiarities which made it impossible for the testicle to emerge. Spence and Scowen (1935) noted that therapy with gonadotrophic hormones caused a hernia to appear during treatment in five cases. They state: 'It seems highly probable that the hernia was present from the beginning and only became noticeable as the testes descended, the hernial sac presumably descending with the testis.' In the present small series it seems that a coincident hernia or a previous operation for one is the strongest factor militating against subsequent spontaneous descent of the testicle. Descent at puberty is highly improbable and surgeons, like Browne, who advise 'in every case operation, at which the co-existing hernia is removed,' are assuredly right.

Spontaneous descent.—Spontaneous descent took place (a) in one bilateral case associated with pluriglandular disorder; (b) in two out of three bilateral cases associated with adiposity and on the left side of the third of these. He had had the right testicle surgically transposed in the scrotum. Descent coincided roughly with the onset of puberty; (c) in the other five bilateral cases, bilateral descent took place in three, on the right at the age of twelve and a half in one, and not in one; (d) in eleven unilateral ones unassociated with hernia, descent was spontaneous in five, was achieved by operation and hormone therapy in two, and in four others no change was noted; and (e) in five associated with hernia or previous operation for it, descent occurred in only one.

Spence and Scowen (1938), speaking of testicles which are examples of the 'superficial ectopic testis,' say skill is needed in the diagnosis of the condition, and after years of study have now been able to define the difference between a testicle lying in the inguinal canal and in the superficial inguinal position. Their criteria are:

- (1) A superficial inguinal ectopic testis lies more superficially than one situated in the inguinal canal.
- (2) When the testis is moved upwards and outwards in the direction of the canal, the superficial inguinal ectopic testis remains in the superficial position and becomes more obvious, whereas one situated in the canal will occupy a position deeper in the canal and thus will become less easily palpable.
- (3) A testis situated in the canal cannot be moved towards the femoral region, whereas this may be possible in the superficial inguinal type.
- (4) When a testis situated in the canal is moved downwards, it will travel in a direct path towards the neck of the scrotum, whereas one

situated in the superficial inguinal region will tend to move slightly lateral to the neck of the scrotum.

My anatomical observations in the past have been chiefly concerned with eliminating the refractile testes from my cases. In future they will be directed along the lines advocated by Spence and Scowen. Yet my observations are highly suggestive that descent has occurred spontaneously at puberty in patients in whom the success would have been attributed to hormone therapy if they had received this treatment. Puberty is in all probability a time when there is an excess of gonadotropic hormones circulating in the blood, as evidenced by the mastitis of puberty in a small number of boys. If this is so, then physicians should develop patience and avoid hormone as well as surgical treatment, both of which are expensive luxuries. This statement is justified by the following facts : (1) A large proportion of testes descend spontaneously at puberty in all types of undescended testicles except those associated with hernia. (2) When descent does take place, the testicles, whether previously bilaterally or unilaterally undescended, develop normally. (3) That at or immediately after puberty, hormone therapy will probably be acting in alliance with an excess of natural hormones.

Armstrong's claim for thyroid extract as an aid to spontaneous descent must now be reconsidered. Dorff recognizes two distinct types of obesity associated with undescended testicles :

- (1) Adiposogenital dystrophy thought to be due to hypogonadism characterized by adiposity, genital hypoplasia, eunuchoid proportions but normal osseous development.
- (2) Masked hypothyroidism with retarded osseous development and hypoplastic testes, in addition to other symptoms of thyroid deficiency.

He has noted that after the exhibition of thyroid : (1) hypoplastic testes increase in size ; (2) undescended testes increase in size and descend to a lower point ; (3) the genitalia enlarge ; and (4) a more rapid response to treatment is noted near puberty.

Hardy (1938b) gave thyroid in connexion with gonadotropic hormone and concluded that it may have enhanced the effect of the gonadotropic principle for the obese patients, but that it seemed of no value to patients of normal build or to those of a feminine build. I have not noticed thyroid insufficiency in any of my cases, nor have I used thyroid except in the first case. Certainly intelligence is on the average well up to normal and in many instances decidedly above the normal. The question must be left sub judice.

Summary

Twenty-four boys with undescended testicles have been observed for from one to seven years. Spontaneous descent rarely occurs in those with associated herniae but does occur in a high proportion of the remaining nineteen at approximately puberty, whether the testicle is unilaterally or bilaterally undescended, and these testicles as judged by the usually accepted standards should be functionally perfect. No harm results from postponing operation

or gonadotropic hormone therapy until puberty, at which time there is possibly an access of natural production of gonadotropic hormone in circulation. Grave coincident disorders—torsion, tumour or inflammation—have not been noted.

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CARDIOMEGLIA GLYCOGENICA CIRCUMSCRIPTA

BY

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In 1932 Pompe first drew attention to hypertrophy of the heart caused by excessive accumulation of glycogen in the heart muscle. Since then experience has shown that such an accumulation of glycogen could indeed explain many of the cases of hypertrophy of the heart in infants, which formerly would have been labelled as cases of idiopathic hypertrophy of the heart, for the enlargement could not be explained by a defect of valve or septum. Later, however, it appeared that there were cases of so-called idiopathic hypertrophy of the heart in infants, without accumulation of glycogen and not showing the typical structure of the cardiac muscle fibres found in cases of cardiomegalias glycogenica (Debré, 1935 ; Mutgeert, 1937 ; Mansens, 1937). There is still a third form of congenital hypertrophy of the heart which clinically appears to be an idiopathic or an essential one. In these cases, however, pathological and microscopical examination prove the existence of defects of the heart muscle, with or without corresponding abnormalities in the coronary vessels (Kugel and Stoloff, 1933). This form is sometimes called the secondary or pseudo-idiopathic form of hypertrophy of the heart.

The question if a sharp separation should be maintained in future between these different forms of congenital hypertrophy of the heart cannot at the present time be answered with certainty. There is some evidence that a relation between the different forms does exist. There is the fact that in cases of pseudo-idiopathic hypertrophy of the heart localized changes in the heart muscle have been found of the same nature as found diffusely spread in the heart muscle in cases of cardiomegalias glycogenica. One observation of such a case has recently been published in the literature ; some time ago we observed an analogous case.

Carrington and Krumbhaar in 1924, under the title 'So-called Idiopathic Cardiac Hypertrophy in Infancy,' described a case of a girl ten months old. Clinically there was a large heart and a palpable liver and spleen. At the autopsy a greatly enlarged heart was found. The origin of the left coronary artery was abnormal ; it originated from the pulmonary artery. Though on macroscopical examination the different parts of the heart had a homologous aspect, the microscopical investigation of the myocardium showed the existence of areas of large waving muscle fibres with 'vacuolar degeneration.' In some

places a slight diffuse fibrosis was found. Staining for glycogen or fat was not performed at that time. After publication of the abnormalities found in cases of the cardiomegalic type of glycogen disease, this diagnosis was considered in the case reported by Carrington and Krumbhaar. In small pieces of the heart muscle of this case, which had been kept enclosed in paraffin for thirteen years, Finkelstein (1936) was able to demonstrate glycogen in the vacuolized areas by means of the carmine stain. Finkelstein was of the opinion therefore that it was justifiable to say that in the case described by Carrington and Krumbhaar there existed localized changes in the heart muscle, which histologically and histochemically showed resemblance to the findings in glycogen disease. Histologically the structure differed from that found in cases of cardiac rhabdomyomas, which also contain much glycogen. In order to differentiate this case from the more diffuse changes found in the myocardium in cases of the cardiomegalic type of glycogen disease, Finkelstein called the condition 'cardiomeglia glycogenica circumscripta.'

Case record

Baby A., a girl, was taken into the Babies Department of the Propaedeutic Clinic of the Wilhelmina-Hospital (director: Prof. I. Snapper) when five months old. She was the first child of healthy parents, born spontaneously and at full term. She had been under regular supervision as regards feeding and general condition. Until some days before admission to the hospital the child had not shown any peculiarity, except that during the previous two months she had gained little weight. Five days before admission she had fallen ill with dyspnoea and laboured breathing; she coughed and whimpered, vomited, perspired abundantly, showed anorexia and a pale complexion, but no fever.

In hospital the child appeared to be ill; she whimpered and had rapid, shallow respiration with active dilatation of the alae nasi. There was no cyanosis and the nutritional state was moderate. The right cheek and upper lip showed remnants of an angioma treated by means of radium. There was marked inspiratory recession of the soft parts of the chest. The heart was greatly enlarged to the right and to the left with loud sounds and a soft systolic murmur, especially at the apex of the heart and just below the sternum. The lungs showed no abnormality on percussion or auscultation. The spleen was not palpable; the liver was enlarged and palpable three fingers'-breadths below the costal arch, and to the left it reached two fingers'-breadths past the middle line. The back of the foot on each side showed slight oedema. The reflexes were normal. The urine contained albumin and urobilin. The sediment contained an occasional erythrocyte and some leucocytes. The blood picture was normal. An x-ray investigation of the thorax (fig. 1) showed a greatly enlarged heart, to the left as well as to the right; in both lungs there were a large number of darker areas (congestion?). Electrocardiogram (Dr. Formyne): P III negative, rather deep S I and S II; T II and T III negative. The fundus oculi showed no abnormality. X-ray photographs of the skull were normal.

The possibility had to be considered of the existence of a glycogen heart as this organ was greatly enlarged without definite evidence of a defect of the valves or other congenital abnormality. Moreover, until admission to hospital there had been no symptoms, a fact which has frequently been observed in cases of glycogen heart. Furthermore, in this stage of the disease the weak murmur did not exclude the possibility of a glycogen heart. The development of the clinical symptoms indicated that the enlarged liver was probably a congested liver.

Certain investigations were performed in order to find other signs as usually found in glycogen-liver (van Creveld, 1928, 1934). The urine on repeated

examination never contained acetone or sugar, and in the blood in the fasting state acetone and β -oxybutyric acid were absent. The fasting blood-sugar was 0.075 per cent. (Hagedorn-Jensen). The glycogen content of the blood in fasting condition was increased (34.5 mgm. per 100 cc.). After injection of 0.25 cc. of adrenalin 1/1000 the blood-sugar content had risen after one hour from 0.075 per cent. to 0.105 per cent.

These observations gave scant evidence in favour of the diagnosis of the cardiomegalic type of glycogen disease. The electrocardiogram was highly suggestive of myocardial damage. The possibility of confirming the diagnosis

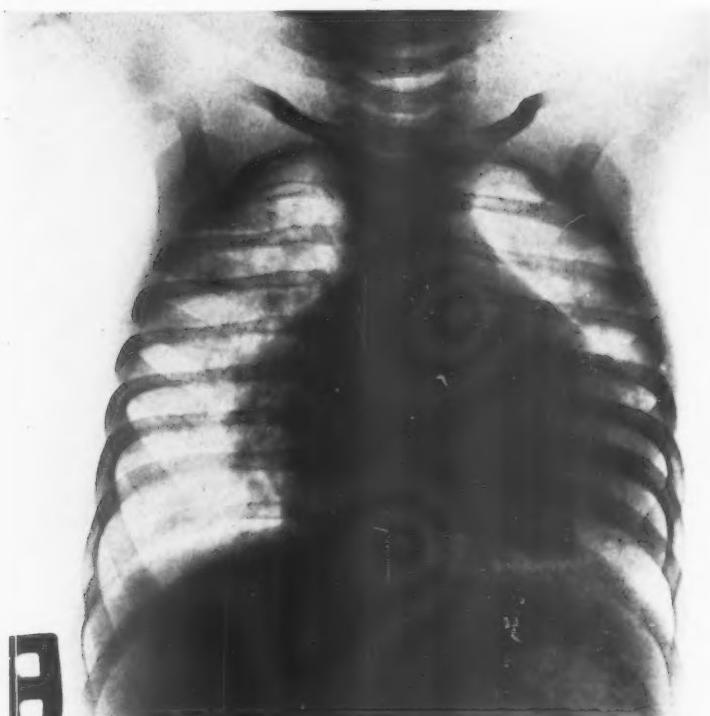


FIG. 1.—X-ray film of the thorax showing the proportions of the heart.

of glycogen disease by examination of some striated muscle fibres obtained by biopsy (Humphreys and Kato, 1934) could not be considered in view of the serious general condition of the patient.

During the nine days of the child's stay in the hospital the oedema of the lower extremities increased; cyanosis and elevation of the temperature remained absent. The von Pirquet and Wassermann reactions were negative. The condition of the heart remained the same, the liver decreased somewhat in size. On the tenth day after admission to hospital the child died suddenly.

At necropsy there was a marked degree of hypertrophy of the heart with a large patent foramen ovale, dilatation of the pulmonary artery-system and peculiar focal lesions in the heart muscle itself, with thickening of endocardium and epicardium. The liver was greatly enlarged, of firm consistency and contained much blood. The lungs were very congested. The kidneys also showed signs of congestion. The adrenals were normal.

It appeared that the diagnosis 'cardiomegalias glycogenica,' already unlikely on account of these findings, had to be rejected when some sections of the heart muscle examined immediately after the autopsy showed no trace of the histological abnormalities characteristic of the 'glycogen heart.' The quantitative determination of the glycogen in a small piece of the heart muscle gave a result of 0·5 per cent., a value which did not resemble the high values found in cases of 'glycogen heart,' but which still was higher than the values usually found at that age in examining the heart a considerable time after death. At this time it was not appreciated how these findings could be fitted together.

The combination of lesions found on macroscopical examination of the

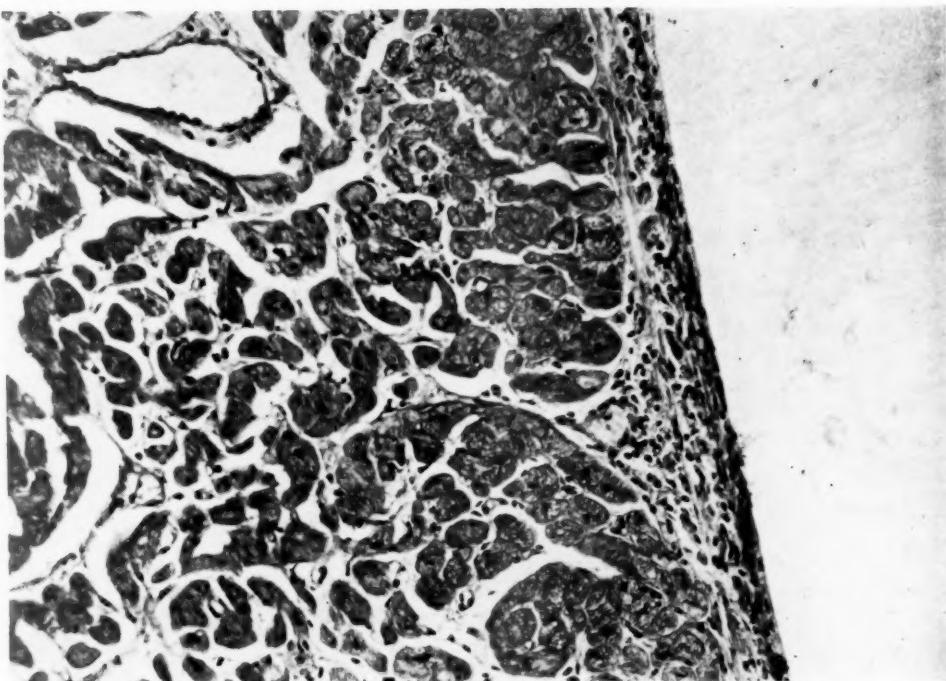


FIG. 2.—Muscle-fibres situated sub-epicardially, showing swelling, granulation and vacuolization of the plasma.

heart and of the pulmonary artery, although rather unusual, has been more frequently observed as a congenital malformation (Joules, 1934; d'Aunoy and von Haam, 1934; Okkels and Therkelsen, 1932). One of us, a short time ago, found this combination of lesions at the autopsy of an adult man. But the present case differed in many respects on macroscopic examination from the reported cases; the hypertrophy of the heart existed on both sides. Further, in this case the heart muscle showed extensive focal lesions, whereas in the reported cases there was at most a slight fibrosis.

MICROSCOPIC EXAMINATION. No abnormality of thymus, pancreas, adrenals, spleen and kidneys was found. Best's carmine stains were negative in these organs. The striated (diaphragm) and the smooth muscle tissues (pyloric muscle, oesophagus and duodenum) showed no abnormalities; in

particular, the stains for glycogen also proved to be negative here. The lungs showed chronic congestion with some dilatation of the branches of the pulmonary artery, even quite near the pleura. The liver showed congestion, with scattered small haemorrhages. Both near the central vein, and more peripherally in the lobules there were a number of small areas in which the liver cells were larger and paler than normal, with sharp outlines of the cells and a fine granular plasma without vacuoles. Stains after Best proved the existence of glycogen in these cells.

In the examination of the heart, epicardium and coronary arteries were normal; the endocardium did not show changes of any importance. In the myocardium there were extensive scattered areas, which were abnormal. In the first place these areas, chiefly under the endocardium, had a structure which

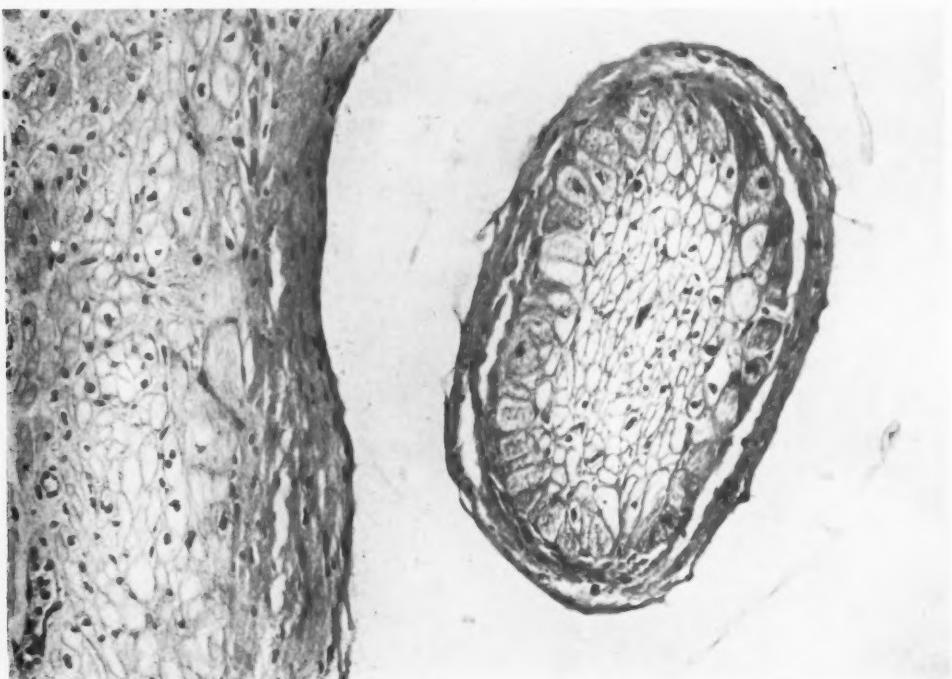


FIG. 3.—Structure typical of the heart-muscle fibres in glycogen heart, in a papillary muscle and in the sub-endocardial part of the myocardium.

is almost characteristic of glycogen degeneration of the muscle fibres: namely, large, long, thick fibres with clear, vacuolar protoplasm. The nuclei lay in the centre, sometimes flattened against the sarcolemma. The borders of these fibres were often distinctly striated. After staining for glycogen only some fibres showed typical, fine-granular drops of glycogen, some around the central nucleus and others more peripherally at the ends of the fibres. The intracellular glycogen granules, however, are present only in those areas where a real glycogen structure is found. Thus any contamination can be excluded (fig. 2, 3 and 4).

The second group of small fields in the myocardium, showing an abnormal structure, consisted of necrotic spots (fig. 5) and muscle fibres with characteristic coarse, globular fatty degeneration, arranged in small groups like forked lightning. Here the glycogen structure is completely absent. There are, however, some fibres which are somewhat swollen, with clear outlines and

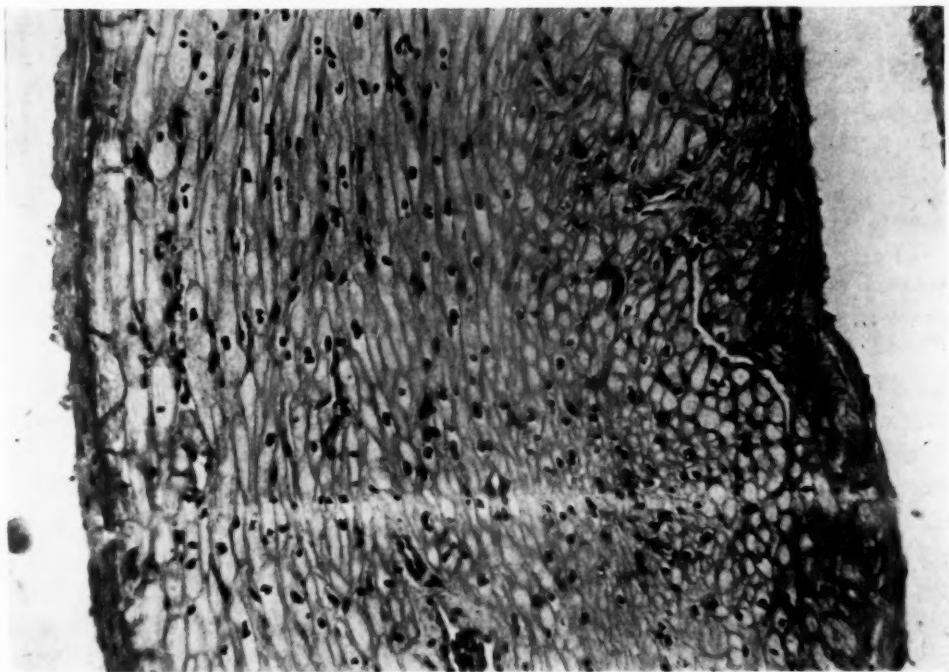


FIG. 4.—Typical vacuolized structure in a papillary muscle ; distinct striation is still present.

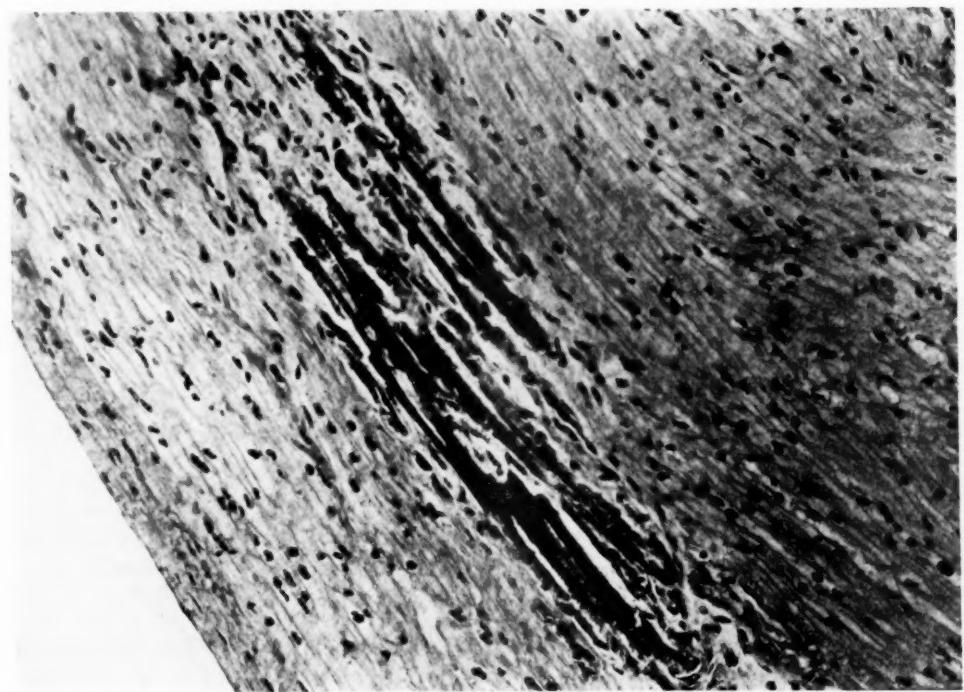


FIG. 5.—Typical necrotic area in the myocardium.

a pale, distinctly granular plasma, with vacuoles (similar to those observed in the case of an adult, in whom there had existed for three hours an obstruction of the big branch of the left coronary artery). Further the myocardium shows small fields of atrophic muscle fibres, where each fibre is surrounded by thickened interstitial tissue ; and a number of small places, made up of thick 'Scholl'-like muscle fibres, which in the haematoxylin-sections take an intensely blue colour and in the van Gieson sections an intensely yellow one. Next to these there are, moreover, small fields (a less distinct passing from one kind into another ?) where the fibres show a coarse structure with absent or very pale nuclei. These fibres take an intensely red colour in the haematoxylin-eosin sections and where the cross-striation is lacking. Finally, in a still more advanced stage, there are small groups of fibres with granulation and a blue-colour in the haematoxylin-eosin-sections.

To summarize the foregoing it may be said that here is a case of hypertrophy of the heart, founded or not on a congenital deformity (the large patent foramen ovale and a dilatation of the whole extent of the pulmonary artery). Combined with these abnormalities there are congenital and (or) acquired abnormalities in the myocardium, namely partial accumulation of glycogen and regressive changes (increase of connective tissue, necrosis, especially fatty degeneration) as a consequence of older or more recent disturbances in the circulation. On histological examination the places where accumulation of glycogen was found showed a striking resemblance to those found by Pompe and others in cases of cardiomegalia glycogenica. In the liver there were small fields with a structure typical of glycogen accumulation (von Gierke, 1929).

Discussion

The following possibilities in explaining the partial accumulation of glycogen as found here have to be considered :

1. The condition results from an unusually dominant development of the conducting system, in which, as is known, at any rate during the embryonic period, analogous structures exist. Most of the abnormalities are, however, not in agreement with this conception. Furthermore, in the case of cardiomegalia glycogenica circumscripta, described by Finkelstein and cited in the beginning of this report, the glycogen fields were not lying especially subendocardially, as in this case.

2. This might be a persistence of the embryonic condition, in which the embryonic structure of the myocardium has for unknown reasons been maintained, especially in the subendocardial area. This would infer that the cases of glycogen heart of Pompe and others would have to be considered—as formerly had been supposed (Pompe, 1936)—as a congenital condition, in which the whole myocardium had remained in an embryonic condition. Looked upon from this point of view, the name glycogen degeneration would be incorrect ; for then there should not be any question of a change of fibres which originally had had a proper structure, but of a persistence of the embryonic structure of the fibres. Why the fibres retain more or less their embryonic state is a question which cannot be answered ; perhaps there exists a relation with some disturbance in the circulation, for in this case there were also many regressive changes which had been caused by a poor circulation. In Finkel-

stein's case also disturbances in the circulation were found (abnormal origin of the coronary artery); however, the regressive symptoms were few (only slight fibrosis). [In the fifth case of glycogen heart discussed by Pompe (1936) (case of Frank-Dykstra) there was a circumscribed accumulation of glycogen and at the same time a defect of the heart (aneurysm of the widely dilated ductus Botalli).] The significance of disturbances in the circulation for the occurrence of glycogen in the heart might be that the proper combustion of the glycogen in embryonic structures, which are rich in glycogen, was disturbed by a poor circulation. At any rate, the occurrence of this accumulation of glycogen—although partial—in a heart which, as in this case, also showed necrosis, fatty degeneration and fibrosis remains very unusual.

3. According to the conception just outlined the circumscribed accumulation of glycogen should represent a further stage in the development of the myocardium than the diffuse glycogen heart. However, this diffuse glycogen accumulation might also be a manifestation of a disturbance in metabolism, and then the circumscribed accumulation of glycogen may be considered to be a stage of recovery. If this hypothesis is correct, the existence of some differences between clinical and anatomical findings in both conditions is quite rational.

All these possibilities can only be solved after extensive research and after further experience of the condition. It is highly probable, nevertheless, that circumscribed accumulation of glycogen with the typical histological appearances in congenitally hypertrophied hearts may prove to be more frequent than at present realized.

Summary

A description is given of a case of cardiac hypertrophy resembling the pseudo-idiopathic type with partial accumulation of glycogen in the heart muscle. On histological examination the areas in which accumulation of glycogen was found showed a striking resemblance to those found by Pompe and others in cases of cardiomegalias glycogenica. In the liver also small areas with a structure typical of glycogen disease were present. Various possible explanations of this 'cardiomegalias glycogenica circumscripta' are discussed.

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TRANSIENT LUNG CONSOLIDATION IN ASTHMATIC CHILDREN* WITH REFERENCE TO EOSINOPHILIA

BY

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The discovery of lung consolidation appearing in rapidly passing attacks in allergic diseases renders possible an important contribution to the group of 'unspecific lung changes,' and an explanation is thereby afforded of a number of pathological lung conditions, the symptoms of which could not be reconciled with those of previously known complaints. Although Löffler of Switzerland has the honour of being the first to describe cases of this type—called by him 'Flüchtige Succedaninfiltrate mit Eosinofili' (1932, 1934)—it appears to the present writer that the most significant contribution has been made by Engel, of Shanghai, who in a publication in 1935 reports as follows :

During the months of May and June a very large percentage of the inhabitants of China are attacked by a peculiar bronchitis which in everyday life is called 'privet cough.' Privet is the name of a species of ligustrum which flowers at the time mentioned. The complaint manifests itself in a cough of moderate intensity, with a scanty, canary-yellow sputum with a metallic taste, which is stated to contain a few leucocytes and microbes. As only inappreciable discomfort accompanies the complaint, which is thought to be associated with the flowering of the above-mentioned plant, a doctor is not consulted.

The complaint has not therefore been investigated to any extent, and accounts of it had probably not been published until Engel did so ; and he would certainly not have had any reason to concern himself with it if he had not been affected by it himself. On this account he had reason to devote greater attention to the complaint and twice made x-ray photographs of his lungs. On both occasions they revealed a massive pulmonary consolidation which completely cleared up after one day, and on another occasion after six days. At the same time the blood showed an eosinophilia between 20 and 25 per cent. with an otherwise normal blood picture. The sedimentation rate was 10 mm. He was completely fit for work. In another person Engel found approximately the same morbid picture with similar transient lung changes. This person, however, showed moderate blood eosinophilia (6 per cent.) ; eosinophilia in the sputum is not mentioned.

* Other suggested names for the condition are Flüchtige Succedaninfiltrate mit Eosinofili (Löffler) and Oedema allergicum pulm. (Engel).

The confinement to a particular season, the transience and the eosinophilia suggested the allergic genesis of the complaint, and Engel suspected the allergen to be material from the flowering ligustrum plant (cf. similarity with ordinary hay-fever). Engel has scrutinized Löffler's cases with regard to the time of their appearance, and finds that they all occurred during June and July, which, in association with other allergic symptoms, arouses suspicions of an analogous etiology.

Engel conceives the lung changes as a Quincke's oedema in the lung, and proposes the designation 'oedema allergicum pulmonis' for the disease. Therapeutically—if any remedy at all be required—calcium lactate in a dose of 3 grammes per diem is recommended.

Löffler has summarized the symptomatology of the disease as follows (1934) :

Weiche, gleichmässige, zum Teil aber auch fleckig-streifige Schatten beliebiger Lokalisation, manchmal rasch verschwindend und an anderer Stelle wieder auftretend, gelegentlich in Mehrzahl vorhanden. Die Schatten verschwinden innerhalb von 8–14 Tagen. Charakteristisch ist das oligosymptomatologische klinische Bild. Der akustische Befund ist sehr gering : keine Dämpfung, selten Knistern, Reiben. Leukocyten : 4–8000. Charakteristisch ist die Eosinophilie, die bis 66 per cent. steigen kann. Die Eosinophilie bietet einen Hinweis, auf anaphylaktoide Prozesse. Senkung etwas erhöht. Subjektive Beschwerden gering, etwas Husten, wenig Auswurf.

In Sweden Hansson (1934) and Eckerström (1936) have published contributions on the question. I discussed the problem in a paper in 1936, based on eleven cases of transient, probably allergic, lung consolidation in adults. I pointed out that when making the diagnosis of allergic lung consolidation too much significance should not be attached to an increased eosinophilia, which may be temporarily or entirely absent, but more to general allergic symptoms, such as asthma, asthmatic bronchitis, hypersensitivity reactions, and local symptoms, such as sputum-eosinophilia. Eosinophilia in the blood may be disguised, reduced or eliminated by the presence of the infection, with fever, which gave rise to the asthmatic bronchitis or the attack of asthma. Asthmatics fall ill with fever and have asthmatic attacks without an increase of eosinophils in the blood, in certain cases the eosinophilia again coming into evidence after the fever and the infection have subsided. Examples have been met in which the eosinophil count rises from zero on the day of admission to 20 per cent. after some days—but one type of child never shows a blood eosinophilia in spite of relatively long periods of observation. (Case 3 and the case described in connexion with it may be sufficient examples of this.) The difficulty of obtaining sputum specimens from children (a gastric lavage specimen would hardly be representative) has prevented the study of the strictly local eosinophilia (i.e. in the sputum) in these 'eosinophilic' cases. In one case of asthma without eosinophilia (case 3 below) a very definite but transient sputum-eosinophilia was shown. In several other cases I have been able to prove that the eosinophilia in the blood does not run a parallel course with the local eosinophilia. The chief significance of an eosinophilia is probably a reaction

against a protein which is foreign to the species, and at the present time the allergen must certainly be considered to be protein in nature. But other allergen substances (carbohydrates, for example) may exist, and nothing is known of their capacity to give rise to an eosinophilic blood picture. It is possible that different protein allergens may cause different degrees of eosinophilia.

I have already pointed out the 'unreliability' of eosinophilia in children in a paper in 1935, describing a number of less common pulmonary and pleural complications in asthmatic children. An account is there given of a group of five children with transient lung changes, which could not be interpreted as due to ordinary non-specific or specific pulmonary diseases, since the patients were afebrile and tuberculin negative. I did not venture at that time to describe these cases as of the same type as Löffler's on account of some differences in symptomatology. Thus four of my cases had symptoms of bronchitis, which Löffler's did not exhibit; eosinophilia had not been demonstrated in all of them. Further, Löffler interpreted his cases as being due to some sort of abortive bronchopneumonia or 'Frühfiltrat,' not emphasizing the possibility of an allergic genesis, and differing greatly from my conception of my own cases. Now, when experience in the subject has been considerably increased, I do not hesitate to include at least four of them (1, 3, 4, 5) as cases of 'transient lung consolidation in asthmatic bronchitis,' which I consider to have mainly the same basis—allergic—as the cases in adults described by Löffler and Engel, although they may have reacted to other allergens. How these allergic lung manifestations were brought about from a mechanical point of view is another problem. It is not unreasonable to suggest that the cause lies in a stagnation of secretion combined with bronchial spasm, resulting in collapse of the lung.

With regard to the nature of the allergen, it is of interest to mention that recently infected tuberculin-allergic patients may possibly react with transient lung changes, which are thus not true bacillary infiltrations but tuberculin-allergic lung manifestations of the same class as non-specific transient lung consolidations. This process is analogous to that in asthma cases with bacterial allergy. Leitner's (1936) cases of transient lung infiltrations in a group of tuberculous sanatorium patients may perhaps be considered in this light. The occurrence of genuine tuberculous bacillary infiltrations of such transience must otherwise be regarded as a new discovery, though one for which Leitner has given no conclusive or even probable proof.

Case records

Two of the cases described previously (1935) will be briefly recapitulated here in the light of modern possibilities of interpretation and widened experience.

Case 1. Lilian K., born 1930. (Case records : 606/33, 281/34.) Since 1932 the patient had been troubled with relapsing bronchitis, for which the medical practitioner had been consulted five times during the autumn of 1932. At the first examination, in August, 1933, a typical asthmatic bronchial catarrh

was diagnosed (emphysematous thorax, added sounds on auscultation and wheezing in the chest with prolonged expiration. Many sibilant and sonorous rhonchi and loose râles diffusely over both lungs). The tuberculin test was negative and the child was afebrile. Her tonsils were removed in September, 1933. There was no improvement in the bronchitic trouble subsequently. Between October 18 and October 22 a period of swinging fever occurred. She was admitted to the hospital on October 22. Except on the day of admission, she was completely afebrile; on admission she exhibited signs of a pharyngitis and the findings in the lungs described above, which still manifested an asthmatic bronchitis. There was no definite dullness and no clinical signs of bronchopneumonia. The Mantoux tuberculin reaction was negative (1 mgm. O.T.). She was now subjected to an x-ray examination for the first time (October 23), which gave the following result: in the right hilus a massive consolidation and in the upper posterior part of the right lower lobe a similar massive parenchymal shadow. The heart was displaced slightly to the right, the upper interlobar limit somewhat drawn down, but the position of the diaphragmatic arch was normal. Atelectasis was probably present. The patient was given an appointment for further x-ray examination on November 4, but neglected to come until later, and the next roentgen examination was made on December 27, 1933. It was then observed that the right-sided consolidation had disappeared, but that a left-sided hilar consolidation with a gland shadow had appeared instead. Outside, in the anterior-lateral parenchyma and centrally, there were streaky and reticular parenchymal shadows, wedge-shaped in the lateral view. At the time of the examination the patient was completely afebrile, but coughed and exhibited a moderate amount of added sounds in the lungs. During the first few months of 1934 the patient improved, and at times the bronchial catarrh entirely disappeared. She increased in weight and was still free from signs of fever or infection. X-ray examination on April 9, 1934, showed a quite surprising and considerable relapse on the right side, in that the hilar changes were more clearly pronounced and a wedge-shaped shadow between the lower and central lobes had appeared. Blood examination showed 10 per cent. eosinophils. The Mantoux reaction was negative (3 mgm. O.T.). (Gastric lavage specimen injected into guinea-pigs was negative.) Sedimentation rate 10 mm. The girl continued to enjoy unusually good health and was without any noteworthy symptoms, and after a week (April 16) a fresh x-ray photograph was taken. The right-sided parenchymal shadow had disappeared, but a dense area the size of a farthing was now observed in the left lung at the level of the fourth rib. This had disappeared by April 30. Eosinophilia was then $2\frac{1}{2}$ per cent. Sedimentation rate 3 mm. The girl has subsequently enjoyed fairly good health, and x-ray pictures have revealed nothing of particular note. Since June, 1935, she has not been re-examined.

Case 2. Wiel H., born 1928. (Case record: 630/32.) During the autumn of 1932 she had repeated bronchial trouble. She was admitted for observation and examined by x-ray on December 27, 1932. A massive consolidation was found in the lower part of the upper lobe with a slight displacement of the heart to the left and a retracted interlobar furrow. The girl was quite afebrile and her general condition unaffected. The Mantoux reaction was negative (5 mgm.). There were signs of emphysema in the lungs with râles and a slight dullness over the central posterior lateral part of the left lung. The patient was examined by x-rays on February 13, 1933, and the consolidation referred to had then disappeared entirely. The girl's bronchitis developed later into asthmatic bronchitis with typical attacks. No estimation of eosinophilia was made at the time.

Unfortunately it has only been possible to bring the two cases described into the discussion as an afterthought, as at the time when the patients were under treatment we did not know of or consider the possibility of allergic lung consolidation. From a differential diagnostic point of view bronchopneumonia may possibly be considered in the first case. In that case it gave no physical signs, which is somewhat remarkable in view of its extent. Nor is the swinging fever for four days typical, and the x-ray picture is hardly compatible with a pneumonia, which must remain an unlikely diagnosis. Finally, the later remarkable changes between left- and right-sided shadows observed by x-rays, without clinically corresponding findings, certainly cannot be accounted for by bronchopneumonia. The patient's asthma and eosinophilia of 10 per cent. are certain signs of her allergic disposition.

The other patient's relapsing bronchitis and emphysematous thorax excited suspicions of allergic causes as early as the autumn of 1932, and these were verified later. Her rapidly disappearing lung consolidation, which does not prevent her from being up and about, her afebrile and unaffected general condition, hardly allow of any other explanation than allergic lung consolidation.

As far as I can find, these two patients are the first cases which have been described in the literature of Löffler-Engel's disease in children, or at least they may, with a high degree of probability, be suspected of belonging to that group. One case of allergic lung consolidations, which appears perfectly definite and which was diagnosed early and satisfactorily followed by x-ray, is afforded by the following recently observed patient.

Case 3. A twelve-year-old girl, previously unknown to us, was referred to the hospital with a severe and typical attack of asthma. From the history it appears that the patient had, during the preceding six months, relapsing bronchitis of an asthmatic nature, but without attacks of asthma; this was probably now followed by an infection of the air passages. She had her

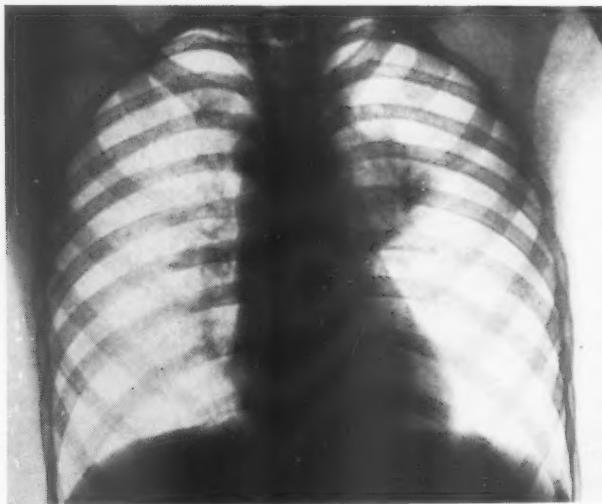


FIG. 1a.—February 26, 1938.

tonsils removed in December, 1937, and was subsequently worse rather than better. The asthmatic attack we are now concerned with occurred on February 25, 1938, and she was nursed at the hospital from February 25 to March 19, 1938. The patient had a low pyrexia on admission, but her temperature soon fell to normal. The sedimentation rate was 25 mm. on admission, and after fourteen days 11 mm. After the asthmatic attack had subsided the patient was entirely unaffected and without discomfort, apart from a certain expiratory dyspnoea.

LUNG FINDINGS : Pronounced bilateral emphysema, no absolute cardiac dullness. On February 25/26 centrally above second and third left intercostal spaces there was a definite dullness and strikingly harsh inspiration with numerous harsh râles, which appeared to be very superficial, resembling



FIG. 1b.—February 26, 1938.

pleural sounds. There was no altered bronchophony. Elsewhere there were diffuse isolated sibilant rhonchi. X-ray examination on February 26 revealed a massive consolidation in the left lung, in the antero-posterior view lying centrally outside the upper hilar area. In the lateral view the consolidation appears as a triangle with the base against the anterior thoracic wall (see fig. 1a, 1b). On February 28 the physical change had disappeared, and x-ray examination revealed that the consolidation had also gone, but instead an induration of the central lobe of the right lung was observed (atelectasis) (see fig. 2a, 2b). On physical examination, there were scanty signs over the seat of the induration, slightly weakened respiratory sounds, and small harsh râles at the right base. On the following day (March 1) the induration of the central lobe had cleared up considerably, but was still observable (fig. 3). On the next day it had almost completely disappeared.

Adrenalin, given intramuscularly and by inhalation, had no definite effect

on the consolidated areas. The patient received an adrenalin injection on admission, which, as appears from the above, did not prevent the lung changes.

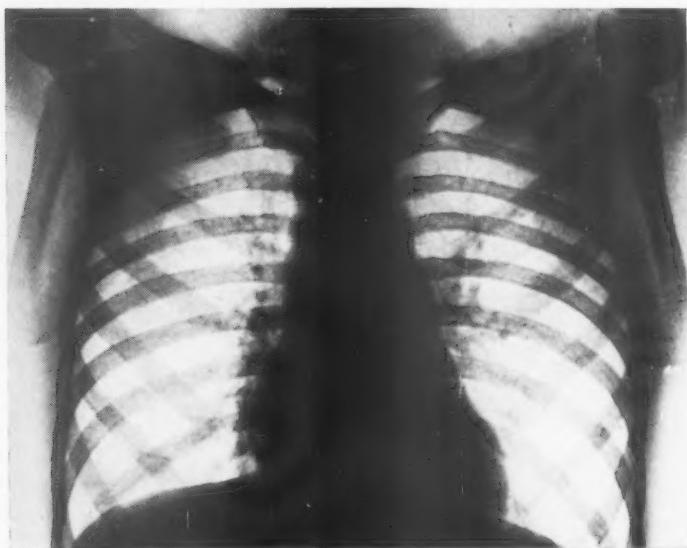


FIG. 2a.—February 28, 1938.



FIG. 2b.—February 28, 1938.

On March 1 the patient was made to inhale a spray of adrenalin solution (1/1000), followed by x-ray examination after an hour or so. There was no appreciable difference in the x-ray pictures.

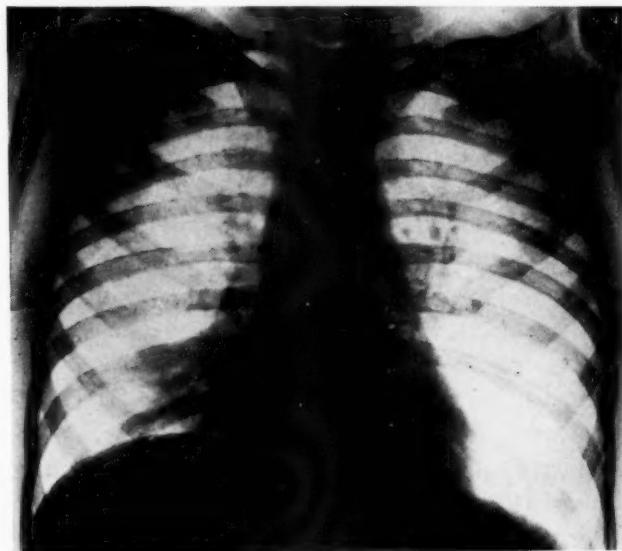


FIG. 3.—March 1, 1938.

BLOOD PICTURE :

		White blood corpuscles	Eosinophils
Feb. 28	..	9,400 per c. mm.	3.7 per cent.
March 2	..	14,300 "	4 "
" 4	..	7,600 "	4.3 "
" 7	..	11,800 "	2.3 "
" 12	..	9,000 "	4 "
" 15	..	9,300 "	3 "

Qualitatively the picture was otherwise normal.

SPUTUM : Specimens obtained on March 3 and 4 showed numerous eosinophil cells on the first day, which had largely disappeared on the second day.

TUBERCULIN TEST : Mantoux 1 mgm. negative.

A discussion of the differential diagnosis in this case is hardly necessary. The allergic illness and extremely transient lung consolidations afford a clear diagnosis. As has been mentioned previously, it may be suspected that the asthmatic lung consolidations are conditioned by atelectasis, a fact which has been further emphasized by the lateral x-ray pictures (see figs. 1b, 2b.) The absence of blood eosinophilia but the presence of a dominating number of eosinophil cells in the sputum is interesting. It should be observed that, during her three weeks in the hospital, the girl did not on any occasion exhibit a higher blood eosinophilia than 4 per cent.

With regard to the eosinophilia, the following case (case 2 in the 1935 paper) is analogous to the previous one.

Ulla-Brita, J., born 1929, has had since 1931 an almost continuous hacking cough, which is periodically accentuated, but unassociated with attacks of asthma. Owing to increased symptoms the patient sought medical advice, and proved to be tuberculin negative and afebrile ; she exhibited signs of a diffuse bronchitis, with slight emphysema and diffuse, bilateral sibilant rhonchi. X-ray examination revealed a non-transient basal opacity (bronchiectasis with atelectasis ?). The condition reacted extremely well to potassium iodide.

There was no increased blood eosinophilia. The diagnosis of 'asthmatic bronchitis ?' was made, and was verified some months later ; the patient was then admitted with a severe and typical attack of asthma, and subsequently had a relapse. She was treated in hospital for two months (partly for social reasons), when repeated eosinophilia determinations were made (at first twice a week). Apart from a single value of 8 per cent. after seven weeks at the hospital, no pathological increase in the number of eosinophil leucocytes could be established.

Differential diagnosis

Differential diagnosis does not afford many possibilities in cases of allergic lung consolidations which have been thoroughly examined. A diagnosis which is often resorted to is 'abortive pneumonia.' I consider that this diagnosis constitutes a lumber-room into which are thrown all sorts of indefinite and unspecific lung cases. In view of the extraordinarily typical and well-defined morbid picture afforded clinically by bronchopneumonia, it appears to me to be somewhat of a contradiction in terms when practically everything characteristic is absent. It would be better for the time being to reserve the diagnosis 'bronchopneumonia' for patients who have had fever for several days and are unfit for work, in which cases physical manifestations (inspection, percussion, auscultation) usually give the classical findings at once, sometimes later (e.g. central bronchopneumonia), and, if an x-ray examination has been made, it reveals a corresponding parenchymal consolidation ; in these cases, moreover, the history is generally characterized by acute onset, shivering, and stained sputum. (We must possibly make an exception here for anergic individuals.) If the case diverges from the clear and classical picture, it is necessary to examine more closely the history and laboratory findings, and to turn attention from the one particular organ. The proving of allergic lung consolidations implies increased resources of differential diagnosis, and it would probably be in better accord with sound medical common sense to make the diagnosis of allergic lung consolidations rather than inflammation of the lungs in the case of patients with allergic manifestations and rapidly transient lung consolidations, whose daily activities are nevertheless unaffected and who enjoy relatively good health. Reconsideration of the diagnosis is necessary if, owing to relapses, the patient again seeks advice.

Bronchiectatic cases sometimes present difficulty. Before the symptoms have become clinically stable, they may show a somewhat variable and indefinite picture. Sometimes, for instance, they cause lobular atelectasis, which at times clears up very rapidly. (The middle lobe of the right lung appears to be particularly liable to be affected.) Another difficulty is that in these bronchiectatic cases there is often an asthmatic element in the lung symptoms. As has been pointed out previously (1935, 1936), this may possibly be ascribed to bacterial allergy due to the infecting organisms present in the dilatations of the bronchi in acute attacks, i.e. sensitive phases. Moderate fever is then met with, usually an increased sedimentation rate and a diffuse bronchitis, which is often localized in both lungs and may be of asthmatic type, accompanied by tightness, wheeziness and murmurs in the chest, signs of emphysema and numerous rhonchi. Some of the symptoms may disappear rapidly, when the

patient enters the de-sensitive phase. Far and away the best diagnostic aid for the bronchiectatic group is the bronchograph. It may be difficult, however, to determine whether the asthmatic bronchitis is primary or secondary to the bronchiectasis.

Conclusions

Transient allergic lung consolidation is a well-defined diagnosis in typical cases, but is one which calls for x-ray examination. In complicated cases the diagnosis is substantiated in the first place by the transient nature of the condition (usually a matter of hours). If the condition persists for a matter of days, the diagnosis becomes more and more uncertain. Secondly, it is necessary that the case should show an allergic disposition, either by exhibiting eosinophilia or other allergic manifestations, such as asthma and evidence of hypersensitivity. The absence of eosinophilia in the blood does not necessarily exclude the diagnosis, nor does the presence of pyrexia and disturbance of general health. This is particularly true of the asthmatic types, in which an infection of the upper air passages may give rise to an attack of asthma, which in its turn causes transient consolidations. In the absence of repeated examinations, the transient nature of the consolidation may not be recognized, and in this the practitioner will sometimes have an advantage over the out-patient physician.

The disease is thus not only theoretically interesting, but provides a differential diagnosis which explains a large number of atypical bronchopneumonias and so-called one-day-pneumonias, and even of so-called 'rapidly recovering tuberculous cases' in patients who are tuberculin-positive or suspected of tuberculosis. An acquaintance with transient lung consolidations appears to be of the greatest importance in connexion with the allergic complaints most generally met with, namely asthma and asthmatic bronchitis. These asthmatic conditions are often sent for x-ray examination. The transient shadows in asthmatic children are prone to appear in the form of massive indurations of atelectatic type, probably conditioned by bronchial spasms, with stagnation of secretions. They vary very much in size and localization.

In view of the evidence that has been brought forward, Löffler's definition of 1934 will require some slight modernization. The transience of the consolidation should be more stressed, the eosinophilia in the blood less so. The occurrence of the complaint in asthmatic persons should be emphasized, as also the possibility of a simultaneous infection, which may change the blood picture, the sedimentation reaction and the general condition.

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THE RELATIONSHIP BETWEEN ACUTE RHEUMATISM AND STREPTOCOCCAL ANTIFIBRINOLYSIN

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That haemolytic streptococci of human origin produce a substance capable of liquefying human fibrin was first demonstrated by Tillett and Garner in 1933. The fibrin from patients recently recovered from haemolytic streptococcal infection was in many cases found to be resistant to the action of this fibrinolysin.

Further work (Tillett, Edwards and Garner, 1934; Tillett, 1935) amplified and confirmed these preliminary observations, and demonstrated antifibrinolysin in the blood of about seventy-five per cent. of patients recovering from acute streptococcal infection. The time of appearance of antifibrinolysin in the blood varies in different patients and in different types of infection. Thus Tillett found that in some cases it was present at the time of recovery, but that in others its appearance was delayed for two to four weeks after the acute infection. There was a suggestion that it developed earlier in cases of erysipelas than in those with an acute streptococcal pharyngitis. These observations were confirmed by Myers, Keefer and Holmes (1935), who also showed that the resistance of the plasma to fibrinolysin, once developed, persisted for a varying time, and Spink and Keefer (1936) found that in erysipelas antifibrinolysin can be demonstrated from eight to a hundred and fifty days after the attack. Waaler (1936) found that patients with scarlatina did not all develop antifibrinolysin, and that in those who did, it might first appear from one to five weeks after the infection, similar observations being made by Stuart-Harris (1935, *a* and *b*). From this work it is now clear that it is rare for antifibrinolysin to be present in the blood unless the patient has comparatively recently experienced a streptococcal infection. The occasional cases to the contrary can be explained by assuming that the antifibrinolysin has persisted long after the infection to which it is due has been forgotten. Antifibrinolysin ranks with antistreptolysin as one of the antibodies produced as part of the immunity mechanism following infections with haemolytic streptococci. The presence of these antibodies in the blood does not necessarily run parallel, and Stuart-Harris (1935*b*) has shown that there is no correlation between antistreptolysin and antifibrinolysin except that when the fibrin is completely resistant to fibrinolysin there is usually some rise in the antistreptolysin titre.

Shortly after Tillett and Garner's original reports, Hadfield, Magee and Perry (1934) found that the fibrin of many patients in the active stage of acute rheumatism was partially or completely resistant to fibrinolysis. This was regarded as further evidence of the frequent occurrence of a haemolytic

streptococcal infection before the onset of an attack or relapse of acute rheumatism. This observation on the occurrence of antifibrinolysin in acute rheumatism has been confirmed by McEwen, Alexander and Bunim (1935), Myers, Keefer and Holmes (1935), Stuart-Harris (1935), Tillett (1935) and Waaler (1936).

It therefore appeared desirable to determine, as far as possible, the precise relationship of the development of antifibrinolysin to the onset of acute rheumatism. For this purpose a large number of patients with acute rheumatism has been studied during the past three years by repeated observations of the antifibrinolysin content of the blood during acute attacks of rheumatism, during convalescence, and following upper respiratory infections with haemolytic streptococci.

Method of investigation

The method used has been essentially that described by Tillett and Garner (1933) and described in the paper reporting the original observations of Hadfield, Magee and Perry (1934). In order to obviate the danger of the organisms losing their fibrinolytic power on subculture, tests on every plasma were made using four different strains of organisms of known fibrinolytic activity and when, on subculture, any of these strains lost its power to produce adequate amounts of fibrinolysin it was replaced by fresh fibrinolytic strains. Two strains, both isolated from cases of puerperal septicaemia and kindly provided by Dr. L. Colebrook, have retained their fibrinolytic activity throughout the period of study despite repeated subculture. As a further check known susceptible plasma was retested with each fresh batch examined. One of the difficulties in working with fibrinolysin is the absence of any standard or numerical titre such as that devised by Todd for streptolysin estimations. An attempt has been made to indicate antifibrinolysin content of the blood by giving those plasmas which were completely resistant to fibrinolysin after twenty-four hours' incubation an arbitrary value of six, and those in which complete liquefaction took place in less than one hour a value of one. The intermediate values are shown in the following table :—

TIME OF LIQUEFACTION OF FIBRIN CLOT		ANTIFIBRINOLYSIN VALUE	SIGNIFICANCE
Less than 1 hour	1	Within normal limits.
1 to 4 hours	2	" "
4 to 8 hours	3	Doubtful. " "
8 to 24 hours	4	Definite increase in antifibrinolysin.
Partial liquefaction in 24 hours	5	Marked increase in antifibrinolysin.
No liquefaction in 24 hours	6	" " " "

Results

A considerable number of the records had to be discarded since during the period under consideration the patients suffered no rheumatic relapse and had no acute haemolytic streptococcal infection. Further patients were excluded as they were not seen until comparatively late in the rheumatic attack, and it is now clear that although in many cases antifibrinolysin, once it has developed

may persist for a considerable time, yet in others it only lasts for one or two weeks. For this reason only those cases of acute rheumatism that came under observation early in the attack have been included in this study. The patients which thus proved suitable for consideration may be divided into four groups.

GROUP A.—This is composed of forty-four cases of acute rheumatism and carditis observed in fifty-seven acute episodes. Nine patients had two attacks and two had three. Thirty-three of these forty-four patients showed resistance to fibrinolysis during the acute stage. In ten antifibrinolysis was present in two attacks (fig. 1) and in the two with three attacks antifibrinolysis was present in all. One patient seen early and right through one attack showed no resistance to fibrinolysis, yet in a subsequent attack this was well marked but lasted less than a month. Thus in fifty-seven attacks of rheumatism in

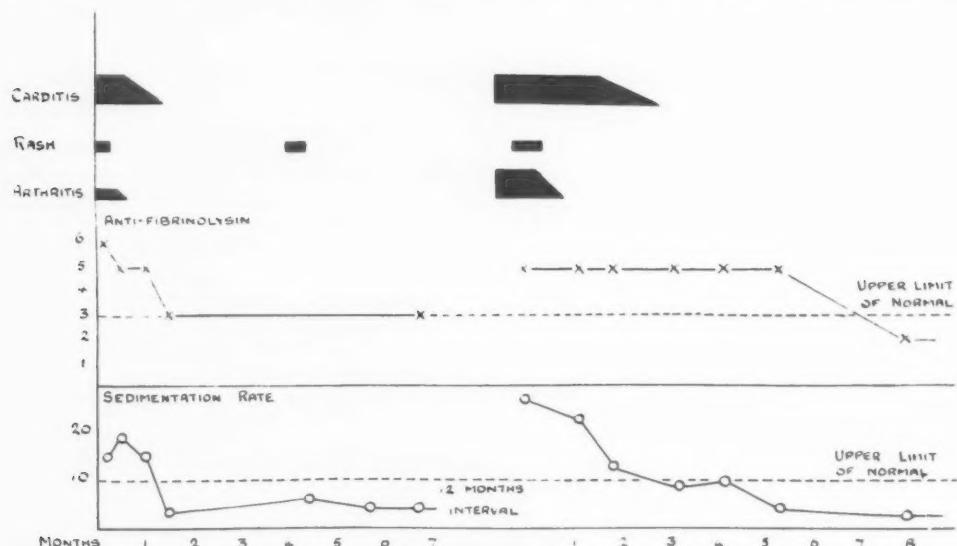
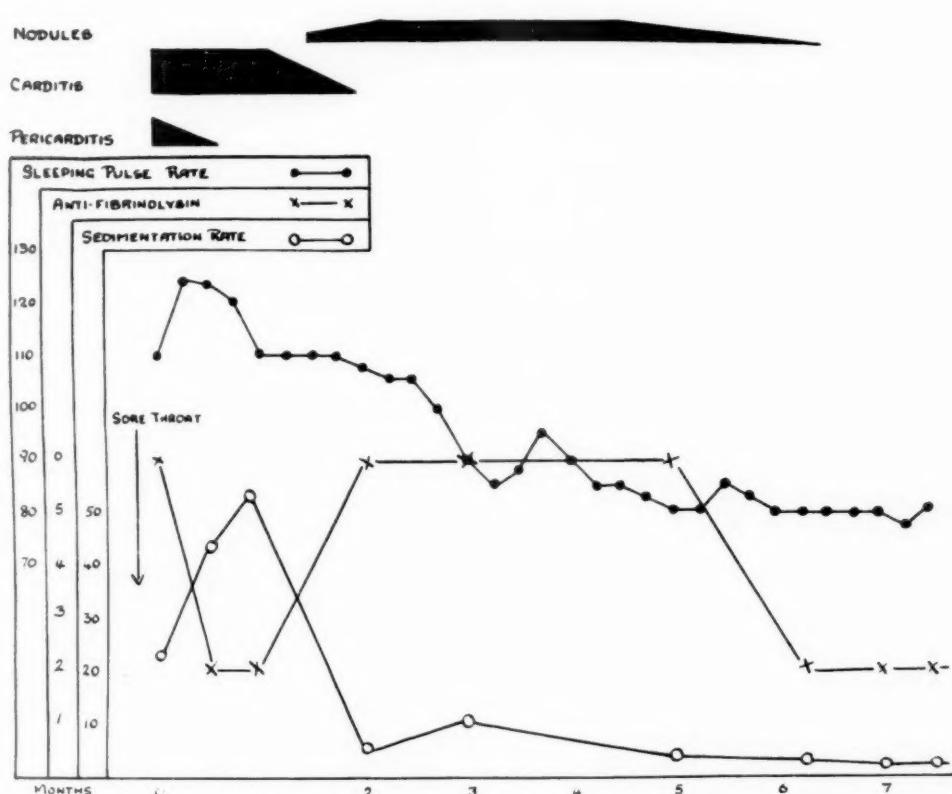
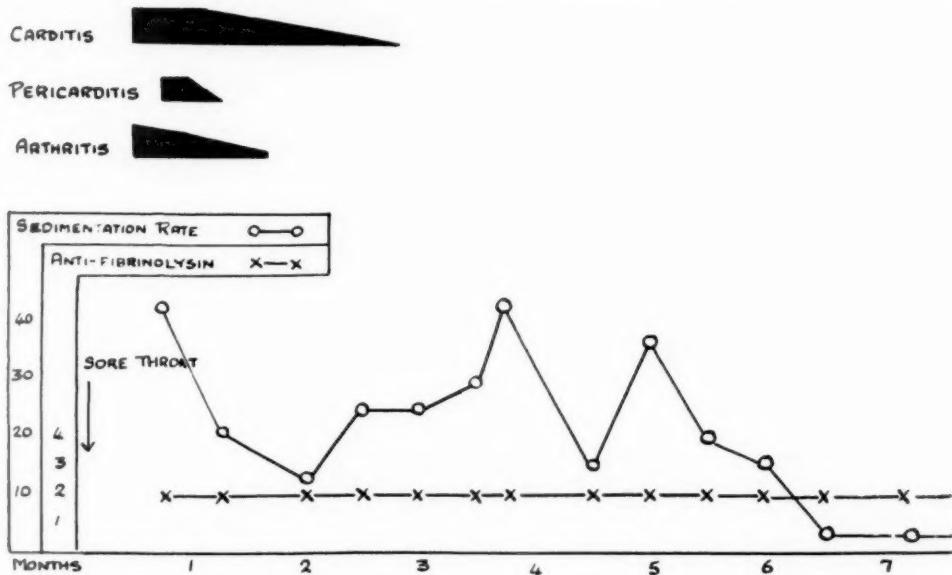


FIG. 1.—A patient observed in two attacks of rheumatism. In both, antifibrinolysis was marked, but in the first it disappeared as the rheumatic activity subsided and in the second persisted long after all activity was at an end.

these forty-four patients, antifibrinolysis was present in forty-five. No obvious difference could be detected in those who showed antifibrinolysis and those in whom this was absent (fig. 2). In one patient with a severe attack of carditis antifibrinolysis was present at the onset of the attack but in the most severe stage of the disease this disappeared only to return as the general condition improved and then lasted for three months, long after all rheumatic activity had subsided (fig. 3). In most instances, resistance to fibrinolysis was most marked at the onset of the rheumatic infection, but in one full resistance did not develop until about a month later. Stuart-Harris (1935a) found that in patients with acute rheumatism antifibrinolysis persisted after the sedimentation rate was normal and other signs of activity had returned to normal. Whilst this occurred in fourteen attacks, in ten the antifibrinolysis returned to normal before the active rheumatic infection had subsided and in the remainder the antifibrinolysis disappeared as the sedimentation rate fell to normal. Thus



of these forty-four cases seventy-eight per cent. showed resistance to fibrinolysin in the acute phase of the disease. This is similar to the seventy-five per cent. of normal people developing antifibrinolysin following uncomplicated streptococcal infection (Tillett, 1935) and is thus strong presumptive evidence that attacks of acute rheumatism are preceded, in the majority of cases, by a haemolytic streptococcal infection even if this is unrecognized. However, it is also clear that the development of antifibrinolysin is not an essential part of the rheumatic process even in the same child (fig. 4).

GROUP B.—This is a small group consisting of six patients with chorea but no carditis. Of these only one showed antifibrinolysin at the onset of the chorea and this lasted for less than a month. Although the number of cases

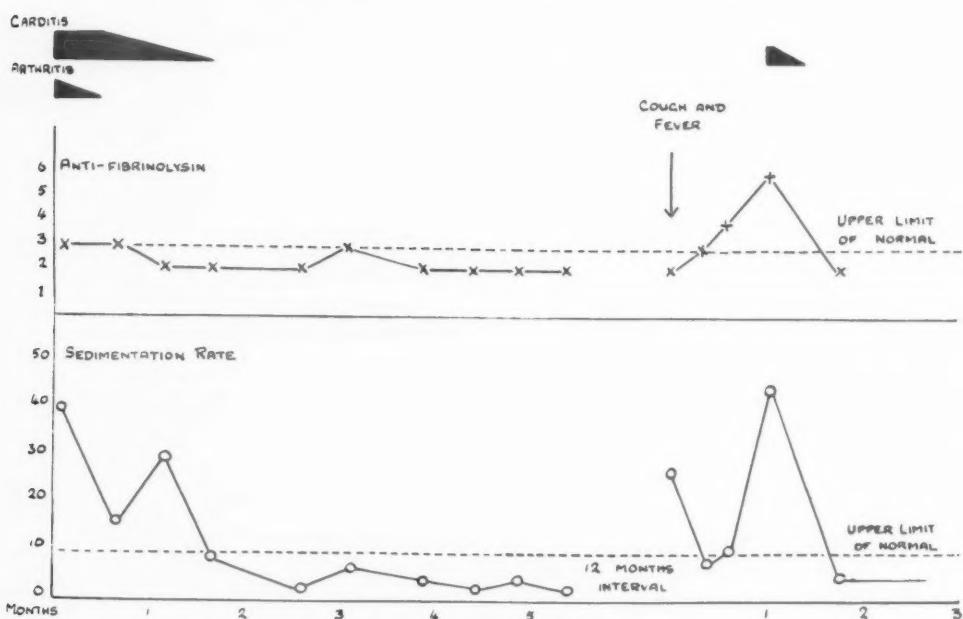


FIG. 4.—A patient with a severe attack of arthritis and carditis showed no definite anti-fibrinolysis, but in a subsequent attack twelve months later this was well marked.

in this group is small, it appears to indicate that chorea is less frequently preceded by a haemolytic streptococcal infection than are the other rheumatic manifestations. This agrees with clinical observations (Perry, 1938).

GROUP C.—This consists of fifteen patients, fourteen with chronic but quiescent rheumatic heart disease and one old case of chorea. While under observation these children developed a haemolytic streptococcal sore throat. There was no definite recurrence of rheumatic infection, but five of the fourteen patients with carditis showed a rise in sleeping pulse rate, which lasted from seven to twenty-one days and which occurred fourteen days to two months after the sore throat. During this time the sedimentation rate was normal and no other evidence of activity was detected (fig. 5). Of the fifteen cases only two developed antifibrinolysin following the attack. In one this appeared three weeks after the sore throat but was not present when the blood was next

examined fourteen days later. The other patient showed resistance to fibrinolysin eleven days after the sore throat and this persisted for two months. The remaining thirteen, including the case of chorea and the five cases showing a rise in the sleeping pulse rate, developed no resistance to fibrinolysin (fig. 5). In three of these resistance had been well marked in the antecedent attack of rheumatism, as was also the case of the child with chorea. All of these fifteen patients received aspirin (thirty grains daily) for six weeks following the sore throat in an attempt to prevent a relapse of rheumatism (Schlesinger, 1937).

GROUP D.—This is composed of ten children with carditis who were observed during a quiescent period and who developed a haemolytic streptococcal sore throat followed by a rheumatic relapse. Six developed resistance

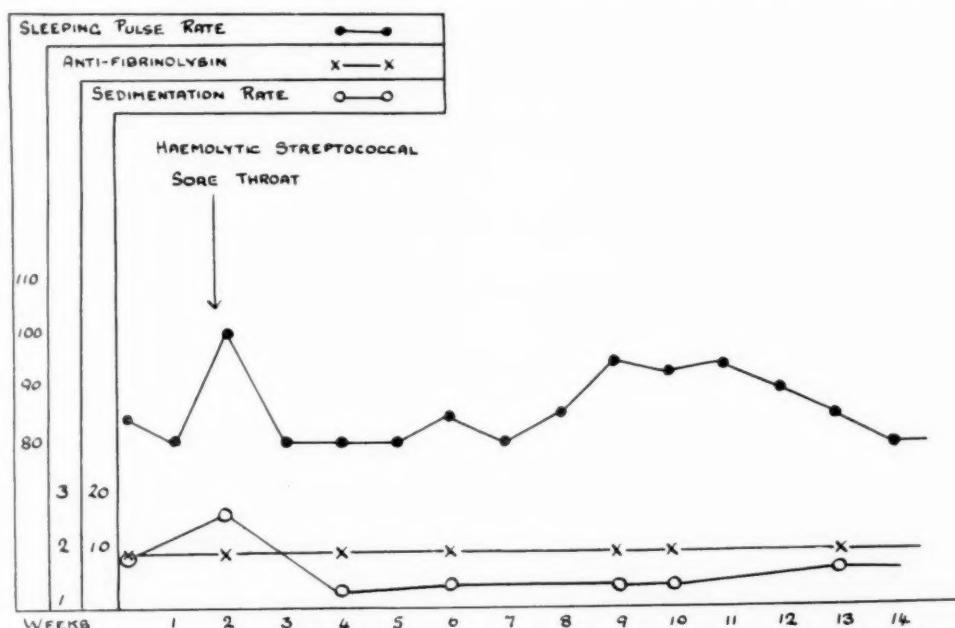


FIG. 5.—A patient with a streptococcal sore throat following which there was no rise in antifibrinolysin and no relapse. (Patient received aspirin for six weeks following the sore throat.)

to antifibrinolysin at the same time as the attack of rheumatism, which was severe in all six and in two fatal (fig. 6). Four failed to show antifibrinolysin, the rheumatic relapse in all four being mild. These four patients received aspirin, whereas only two of the patients in which antifibrinolysin appeared were given it. These findings, especially when taken in conjunction with results found in group C, are at striking variance with Stuart-Harris's observation that resistance to fibrinolysin developed with marked frequency in rheumatic children following a streptococcal sore throat. Schlesinger (1937) has suggested that the administration of salicylates to rheumatic children following a haemolytic streptococcal sore throat tends to prevent relapses. Whether this view is correct or not, the present study indicates that it does tend to inhibit antifibrinolysin formation. This observation agrees with those of Derrick,

Hitchcock and Swift (1928) who found that the administration of salicylates to patients who had received horse serum tended to prevent the development of anti-horse serum precipitin and the arthritis of serum sickness. This possible action of the salicylates in inhibiting antibody formation merits further investi-

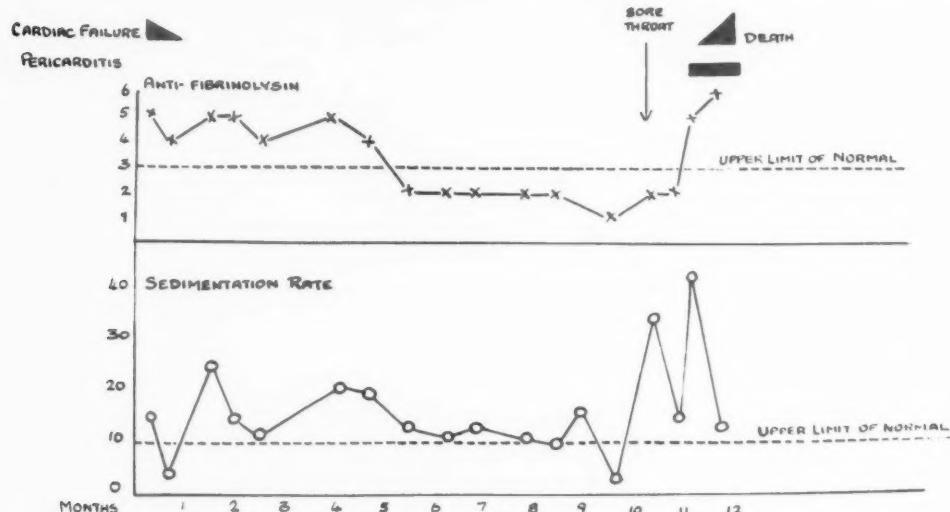


FIG. 6.—A patient with a severe attack of carditis with failure who subsequently developed a streptococcal sore throat followed by a recurrence of carditis which proved fatal. Antifibrinolysin was present in both attacks. (No aspirin.)

gation. Groups C and D thus show that although the majority of patients with a relapse of acute rheumatism following a streptococcal infection show resistance to fibrinolysin, this is not invariably the case. Further, rheumatic patients who develop antifibrinolysin following a streptococcal infection do not necessarily develop a rheumatic relapse.

Conclusions

From this investigation it is clear that the appearance of resistance to streptococcal fibrinolysin in the blood of patients with acute rheumatism is not an essential part of the rheumatic process. Antifibrinolysin is present in about seventy-eight per cent. of patients with acute rheumatism, which is approximately the proportion of normal patients who develop antifibrinolysin following a streptococcal infection. There is no correlation between the duration of antifibrinolysin and the duration of the rheumatic attack or between antifibrinolysin and the severity of the rheumatic attack. There is some evidence that the administration of salicylates following a streptococcal infection inhibits the formation of antifibrinolysin.

Thanks are due to the Colston Research Society of the University of Bristol for a grant which made this investigation possible and also to Mr. W. S. Emery for his technical assistance.

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A STATISTICAL NOTE ON GASTRO-INTESTINAL DISORDERS IN INFANTS

BY

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During the preparation of the Alder Hey Hospital Annual Report for the year 1937 the case records of 1,993 children under one year of age were classified, and those of 539 in the group of gastro-intestinal disorders analysed in detail. The figures obtained are published in the hope that they will prove of use or interest to others undertaking a similar statistical survey.

1,993 children under one year of age were treated in the hospital during the year 1937 (January to December inclusive). They were classified into nine groups :

I.	GASTRO-INTESTINAL DISORDERS	539 cases
II.	RESPIRATORY DISORDERS	643 "
III.	PREMaturity	33 "
IV.	CONGENITAL ABNORMALITIES	53 "
V.	CONGENITAL PYLORIC STENOSIS	15 "
VI.	OTITIS AND MASTOIDITIS	197 "
VII.	SURGICAL CONDITIONS	241 "
VIII.	INFECTIOUS DISEASES	105 "
IX.	OTHER DISEASES	167 "
						1,993 "

Group I, the group under discussion, included feeding difficulties (under- and over-feeding, failure to gain weight, maternal mismanagement), constipation, diarrhoea, minor gastric upsets following vaccination, chill and teething, stomatitis and sore buttocks. The feeding histories of patients in this group were carefully scrutinized : 14 per cent. were inadequately noted and were not classified. The diet of 45 per cent. was highly unsatisfactory in quantity or quality or both, while that of the remainder (41 per cent.) was passed as satisfactory in these respects. In few cases, however, were extra vitamins given. As the figures quoted represent only gross errors in the diet, the impression was gained that the feeding of infants in this class of hospital patient, many being the children of unemployed parents, is most inadequate and urgently in need of supervision. The commonest faults were lack of sufficient protein and the feeding of a too dilute mixture (i.e. of low calorie value) usually in too large amount. As has been said before, vitamin deficiencies in the diet were almost constant.

The state of nutrition was correspondingly poor. The weight was not

recorded in 6 per cent. of cases, either because the child was too ill to be weighed or because it was over the age of nine months, after which the weight record is not kept as a strict routine. The remaining 94 per cent. were divided into three groups :

Athreptic (more than 40 per cent. under expected weight)	15 per cent.
Hypothreptic (20-40 per cent. under expected weight) ..	34 "
Satisfactory (within 20 per cent. of expected weight) ..	45 "

Few of those infants classed as satisfactory were of ideal weight, most of the weights tending to be low.

The commonest symptom in this group of cases was diarrhoea. In mild form it accompanied most of the dyspepsias and feeding difficulties, but in 281 cases it was sufficiently severe to dominate the picture. In these cases of diarrhoea, with or without vomiting, the diagnosis of gastro-enteritis was reserved for those with a true enteral infection. Fifty-nine patients (22 per cent.) showed the clinical picture of 'summer diarrhoea,' some cases being fulminating, the remainder of varying degrees of severity. Epidemic features were not constant, but were present in a large proportion of these cases classed as true enteral infections. No light was thrown on the bacteriology of the condition. Cultures from the faeces yielded :

No pathogenic organisms	38 cases
Bacillus of Morgan	15 "
Bacillus Proteus	4 "
Bacillus paratyphosus B	1 case
Bacillus Aërtrycke	1 "

The death-rate in this group was 42 per cent.

One hundred and eighty-nine (67 per cent.) cases of diarrhoea were associated with parenteral infections and other disorders as follows :

Otitis media and mastoiditis	111 cases
Nasopharyngitis	25 "
Pulmonary infections	25 "
Pyelitis	8 "
Teething	4 "
Rickets	2 "
A mixed group (such as skin lesions)	14 "

The death-rate in this group was 50 per cent., but more than three-quarters of these deaths were judged to be due to infections of the middle ear and mastoid. The remaining thirty-three cases (11 per cent.) of severe diarrhoea were thought to be due to primary nutritional disorders.

Discussion

From these figures it appears that the number of cases of true gastro-enteritis is small in comparison with the total number of cases showing a similar clinical picture (in this series 59 : 281). The conviction was produced that the more thorough is the search for a source of infection, the more frequently it will be found to be responsible for the illness of these children. Of 189 cases of parenteral diarrhoea only forty-one were readily diagnosed as such by ordinary

clinical examination in the admission room. The frequency of otitis media and mastoiditis, often latent, as a cause of persistent diarrhoea was well demonstrated. Successful treatment of the local condition resulted in prompt improvement of the general state and amelioration of diarrhoea, but of 111 cases of otitis with the enteritis syndrome, seventy-five died. Post-mortem findings of pus and diseased bone confirmed the diagnosis.

The effect of weight and nutrition on the incidence of this severe toxic type of ear disease was not striking. Forty-seven of the 111 cases were of satisfactory weight, forty-eight being hypothyreptic and sixteen athreptic. All except one of the athreptic babies died, but the condition was almost equally lethal in the other two groups. Operative treatment of these toxic babies with ' mastoiditis occulta ' and severe diarrhoea was undertaken in three cases only, two of whom died. From a previous series of cases treated in this hospital (McConkey and Couper, 1938) the conclusion was drawn that operative interference, apart from paracentesis of the tympanic membrane, did not improve the prognosis. The treatment adopted was that directed toward replacement of tissue fluids and relief of tension in the middle ear. On the other hand, eleven cases of mastoiditis in infants without diarrhoea were operated upon, ten of whom recovered.

The position of the breast-fed baby appears, from these as from all other findings, to be a much safer one than that of the artificially-fed infant. Of 118 babies who died with the enteritis syndrome, ten were breast-fed. Two of these appeared to be cases of true enteral infection, one with the bacillus paratyphosus B. Both were under six months of age, so that the likelihood of mixed feeding was small, and both were said to be entirely breast-fed. The other eight were cases of parenteral diarrhoea.

Summary

1. A statistical survey is reported of cases commonly known as gastro-enteritis, treated in the Alder Hey Hospital during the year January–December, 1937.
2. The presence of a latent infection is suggested as the cause of the condition in a large number of cases.
3. The incidence of true ' summer diarrhoea ' is comparatively low.
4. The diets of infants under one year were found to be, in general, highly unsatisfactory.

Thanks are due to Dr. W. E. Crosbie, Medical Superintendent, Alder Hey Children's Hospital, Liverpool, for permission to publish these figures, and to Dr. Norman B. Capon for his helpful suggestions and criticism.

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THE APPLE TREATMENT OF INFANTILE DIARRHOEA

BY

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Although the beneficial effect of apple in the treatment of diarrhoea seems to have been known for many years, it is only in the last decade that it has found a place in medical literature. Schachter (1934) in one of his communications on this subject refers to a description of apple therapy in dysentery in an English book published in 1775. Apparently the treatment has been an 'old wives' tale' in parts of Germany for many years, and during the last war it was found in a certain concentration camp that patients with dysentery who managed to secure apples growing in the grounds of the camp were quickly relieved of their symptoms.

The recent interest in the diet dates from Heisler's publication in 1929 entitled 'Apple, Sauerkraut, and Buttermilk Treatment of Infantile Diarrhoea.' In the same year Moro published an article entitled 'Apples in diet for the treatment of diarrhoeal conditions in children,' and since then several articles have referred to the treatment as the Moro-Heisler diet. Interest in this subject was at first centred in Germany, but it has now received practically a world-wide trial, and with few exceptions reports have been favourable. The literature up to the end of 1933 has been summarized by Schachter, and a report issued by the American Council on Foods refers to the more important publications up to 1937.

Although the apple diet has produced quite a big literature in Germany and the U.S.A., with contributions also from almost every European country, the Dominions, and Uruguay, little has appeared in the medical literature of this country. Schlesinger spoke of the treatment at the British Paediatric Association in 1936, and a brief précis of his remarks appeared in this journal later in the same year (Schlesinger, 1936). The only other article in this country is from the pen of Barondes, of San Francisco (1937).

A review of the literature indicates that the treatment has been used in practically every type of diarrhoea met with in children. Cases of frank dysentery, of non-specific ulcerative colitis with blood and mucus in the stools, and of parenteral diarrhoea have apparently all been benefited ; even so the treatment is not claimed as a specific cure, but rather as an adjunct to other more customary procedures, sometimes succeeding where other methods have failed. The treatment has also been used in children of all ages down to as young as two or three months.

The mode of preparation differs in different hands. Heisler originally stated that sour apples should be used, Moro advocated ripe sweet apples. Whether or not the peel should be removed is also a matter of opinion, and it has been stated that the apples should be cut up and allowed to stand until turned brown by the air. We are not in a position to pronounce on all these points, for we have not varied our method, a description of which appears later. Nor have we employed a dried apple pulp, traded under the name Aplona, for which success is claimed.

Apple pulp does not of itself contain sufficient water to satisfy a child's fluid requirements, and therefore extra fluid has to be given with the apple. Plain water may be used, others have advised a weak, freshly prepared infusion of tea, and this has been used in the present series of cases. The benefit of the tea is chiefly as a source of fluid ; the small amount of alkaloid in it may perhaps have some stimulating effect, but as the tea is freshly prepared the amount of tannin present is too small to exert a constipating action.

Present investigation

This communication gives the results of treatment in thirty-six babies, of whom thirty-four were treated at St. Giles' Hospital (London County Council), the treatment having been carried out under the supervision of one of us (W. S.).

Cases. The accompanying table gives details of the cases. Twenty-two were males, fourteen females. The age of the infants ranged from nine weeks to two years, the majority being between six and fifteen months. A point which perhaps should be emphasized is that the infants were drawn from a poor class and most of them were anaemic, puny and undernourished by the time of their admission to hospital. It is commonly taught that the initial treatment of infantile diarrhoea should consist of a purge, usually castor oil, provided that the child is not too feeble ; with this in mind, the condition of the infants in this investigation can best be indicated by stating that practically none were judged strong enough to withstand a dose of castor oil.

In most of the infants diarrhoea had been present for at least a week, and although some of them were passing a dozen or more stools a day, more commonly the stools numbered four or five a day and were green, curdled and offensive in character. The cause of the diarrhoea varied. Four infants were regarded as suffering from acute infective diarrhoea, and although they all recovered the impression was obtained that recovery might equally have come

about without recourse to apple. In thirteen the diarrhoea was associated with infective conditions elsewhere in the body, and so was regarded as parenteral ; in this group three infants died, two with an associated bronchopneumonia and the third with eczema and pyelitis. In twelve the diarrhoea was regarded as dietetic, the onset coinciding with weaning from the breast to some patent food or to a more solid diet, or changing from one patent food to another. Only two infants were entirely breast fed ; one developed diarrhoea secondary to bronchitis, the other, the youngest in the series, was a premature and wasted infant. Both improved rapidly after the apple diet, and resumed breast feeding.

Effect of treatment. Apart from the question of recovery, incidental effects were noted during treatment. At the end of twenty-four hours the tongue and buccal mucosa developed a peculiar brown discolouration, appearing as though slightly tanned, and the efforts of the nursing staff to remove this were quite unavailing ; it persisted for at least a week after the apple was discontinued. Although coloured in this way the mouth did not appear to be parched, and sucking was not affected. As to vomiting, those infants who tolerated the diet ceased vomiting almost immediately ; in fact, it was only when an attempt was made to include the peel that vomiting seemed to be aggravated. The effect on the stools was noticeable ; by the end of the first full day's treatment the offensive odour disappeared, and the motions began to be formed and bulky. Their number was also reduced, and by the third day only one or two motions were passed ; in fact, in several infants the diarrhoea was by this time replaced by a mild constipation, no motions being passed for twenty-four hours. Together with this change in the stools, the appearance of toxæmia borne by many of the infants faded out. Their eyes brightened, they became more alert, and by the third day they had regained a good appetite. Another striking feature was the rapid gain in weight made by the majority of infants, often from the first day of treatment.

Dietary technique

PRELIMINARY TREATMENT.—Although many of the cases began their apple treatment within a day or two of admission to hospital, others received a more customary type of treatment for several days, including measures to combat dehydration and a simple fluid diet, and it was only when these had not proved successful that resort was made to apple therapy. Invariably when dehydration was severe, efforts were made to overcome this by subcutaneous or intravenous salines before apple treatment was started.

PREPARATION OF APPLE.—Various sorts of apple were tried, and it was soon realized that a brand with a soft flesh and plenty of juice facilitated preparation. Jonathan apples easily ranked first, followed by Sturmer Pippins and Cox's Orange Pippins. Newton Wonders were not suitable. The apples were peeled and then grated on a fine grater, the pulp and juice being fed as a mash. Each feed was prepared separately so that the pulp had not time to turn brown. At first an attempt was made to include the peel, but even when it was finely cut it seemed to make the infants vomit, and so was discontinued.

CASE NO.	AGE IN MONTHS	DURATION OF DIARRHOEA	TYPE OF DIARRHOEA
1	2½	From birth	—
2	2½	4 days	Dietetic
3	3	3 weeks	Dietetic
4	3½	16 days	Parenteral
5	4	Diarrhoea began in hospital 2 weeks after operation for intussusception	Infective
6	5	1 week	—
7	5	1 week	Acute infective
8	5	4 weeks	Parenteral
9	6	3 days	Dietetic
10	6	—	Infective
11	7	10 days, 18 stools a day	Parenteral
12	7	2 days	Parenteral
13	7	—	Parenteral
14	8	2 weeks	Dietetic
15	9	2 days	Parenteral
16	9	2 days	Dietetic
17	9	—	Parenteral
18	9	2 weeks	Dietetic
19	10	1 week	Parenteral
20	10	—	Dietetic
21	10	2 days	Dietetic
22	10	'A long time'	Dietetic
23	10	10 days	Dietetic
24	11	Diarrhoea began in hospital 8 days after circumcision	Infective
25	11	12 stools a day	Dietetic
26	12	3 days	Parenteral
27	12	8 weeks	Parenteral
28	13	1 day	—
29	13	1 week	Dietetic
30	13	—	Parenteral
31	15	6 weeks	—
32	16	A long time	Parenteral
33	16	10 days	—
34	18	3 days	—
35	22	1 week	Parenteral
36	24	4 days	—

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COMPLICATIONS	RESULTS AND REMARKS
Prematurity and marasmus —	Recovered. Breast-fed. Recovered. Treated with apple-juice, but no pulp. The juice was continued for 4 days.
Twin	Died. At first the infant did well and in the week after apple gained 8 oz. in weight. Then suddenly collapsed. No post-mortem examination.
Bronchitis —	Recovered. Recovered.
— —	Recovered. Recovered.
Pyelitis and bronchitis —	Recovered. Recovered. Recovered. Recovered. Also had blood transfusion.
Fractured femur in plaster	Recovered.
Scurvy	Recovered.
Bronchitis	Recovered. Breast-fed.
Bronchopneumonia —	Died. Recovered.
Bronchopneumonia —	Died. Recovered.
Eczema and pyelitis —	Died. Recovered.
Otorrhoea ; bronchitis — — — — — — —	Recovered. Recovered. Recovered. Recovered. Recovered. Recovered. Recovered.
Otorrhoea	Recovered.
Pyelitis	Recovered.
Convulsions —	Recovered. Recovered.
Boils —	Recovered. Recovered.
Bronchitis — —	Recovered. Recovered. Recovered.
Bronchitis —	Recovered. Recovered.

Feeds were given either by spoon or from a bottle with a large-holed teat, according to the age of the infant, and were spaced at three-hourly intervals throughout day and night. The youngest infants received a teaspoonful at each feed, while at a year the pulp of a whole apple was given, equivalent to eight apples in twenty-four hours. When fed from a spoon the apple was abruptly discontinued after seventy-two hours, but when given from a bottle the pulp had to be diluted with water, and it was then found necessary to continue apple feeding for four days. During the following three days the diet was built up to a full and normal one according to the patient's age.

PREPARATION OF TEA.—In order to bring the fluid intake up to the required level the patients treated earlier in the series were given water with the apple, but later on tea was given instead, and the majority of the patients received tea. Indian tea was used, and was prepared by infusing half a drachm of tea in half a pint of water. The tea was allowed to draw for two minutes only, and was given without milk or sugar. The amount was calculated on the basis of allowing two-and-a-half ounces per pound of body weight per day, the total amount for the day being divided into eight feeds at three-hourly intervals. One hour was allowed between an apple feed and the corresponding drink of tea.

The tea was not discontinued when the apple was stopped, but was fortified by additions of milk and sugar, until after two or three days the tea was omitted and a normal diet resumed.

Mode of action

The rationale underlying the treatment is not as yet completely understood. The most popular theory is that improvement is to be attributed to pectin, acting in virtue of a colloidal and buffering effect which prevents the absorption of intestinal toxins ; these are then excreted in the stools. This seems not to be the whole story, however, for possibly the tannic acid compounds present in apple may have some astringent effect, and in this connexion attention has already been drawn to the browning which affects the mucous membrane of the mouth and tongue. Others have attributed the benefit to malic and other acids present in apple, but this view is difficult to accept, since it has been shown that apple made alkaline by the addition of sodium hydroxide is equally effective.

In a satisfactory case the stools soon become formed and obviously contain a good deal of cellulose residue, but it is difficult to see how the residue in itself can have a mechanical action in checking the diarrhoea ; it would rather be expected that the reverse would happen.

Summary

The effect of a diet of raw apple pulp and weak tea has been studied in thirty-six infants suffering from diarrhoea. Although the treatment is in no sense specific and does not replace other methods, it may be employed as a valuable adjunct. The diet is seen to best advantage in infants with persistent diarrhoea associated with the passage of frequent loose, offensive motions. The most noticeable effects are the lessening of toxæmia, the improvement in the stools and the rapid and sustained rise in weight.

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Thanks are due to the chief medical officer of the London County Council for allowing this investigation to be undertaken and for permission to make this report ; to Dr. A. Randall, Medical Superintendent of St. Giles' Hospital, for facilitating the analysis of the hospital records ; to Dr. Evelyn Mitchell, for supervision of the infants ; and especially to Sister McQuire for her keen interest and close co-operation both in the preparation and administration of the diet.

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VITAMIN-RESISTANT RICKETS

BY

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Since the recognition of avitaminosis D as the paramount factor in the production of true rickets, certain rare cases have been described, particularly by paediatricians in this country and in the United States, in which administration of the vitamin, even parenterally and in enormous doses, fails to produce that healing of the disease which regularly occurs with such therapy in the vast majority of rickety children.

Theoretical considerations

After infancy, rickets appears if the calcium, phosphorus and vitamin D requirements of the growing skeleton become insufficient, i.e. with deficient intake ; in the presence of severe calcium drain without compensatory intake ; with non-irradiation of body ergosterol ; when calcium-phosphorus balance is markedly disturbed ; and lastly if absorption fails to occur from the bowel. Thus, the conditions in which rickets can occur may be tabulated as under :

1. Nutritional :
 - (a) absolute (adverse social circumstances) ;
 - (b) relative (pregnancy and lactation).
2. Lack of sunshine :
 - (a) absolute ;
 - (b) relative (coloured races).
3. Advanced renal disease.
4. Coeliac disease.

But cases are also seen in which none of the above factors seems to operate and the rickets is extremely resistant to vitamin therapy. In such cases the disease remains active until growth has ceased. It is with these vitamin-resistant cases that this paper is mainly concerned. The clinical and radiological picture is that of florid rickets, and the differentiation from the relatively common nutritional type can only be made when the lack of response of the former to therapy is noted. Indeed, it is often a matter of some surprise to the clinician to find that what appears as a simple case of rickets remains stubbornly in *statu quo* despite the exhibition of vitamin D in the usual doses. Enormous doses likewise produce little or no effect upon the condition, and it is only when growth

ceases that the rickets heals. The following cases are illustrative of this rare disease.

Case reports

Case 1. G. P., a boy aged four years, was admitted in May 1936 because he was walking badly. There was no history of diarrhoea and no symptoms suggestive of renal disease. No other members of the family had suffered from rickets or any difficulty in walking. He was a breast-fed child and had had regular cod-liver oil since being weaned.

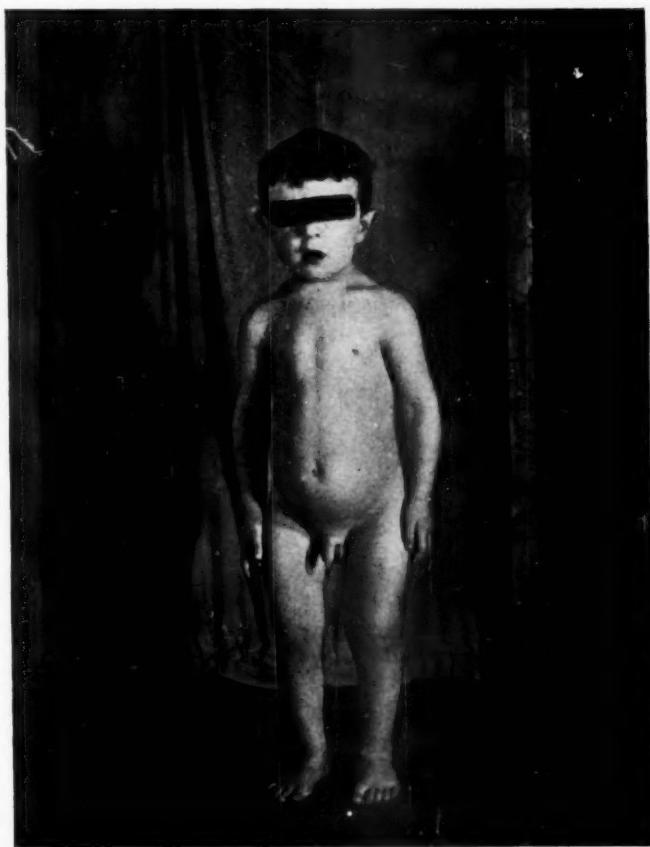


FIG. 1.—Case 1.

ON EXAMINATION no abnormal physical signs were discovered in the cardiovascular, respiratory or central nervous systems. He was of short stature (fig. 1) and presented enlarged epiphyses at the wrist, a rickety rosary and genu valgum. X-rays (fig. 2) confirmed the clinical diagnosis of rickets. The blood calcium was 10.5 and phosphorus 3.1 mgm. per 100 c.c. and blood phosphatase 76 units. The calcium and phosphorus balances were both normal. The total faecal fats were 12.6 per cent. with normal splitting. The glucose tolerance curve and fractional test meal were both normal, as was a complete blood count. Blood analysis gave a normal figure for urea, and uroselectan x-rays of the renal tract were normal, while a Van Slyke urea clearance test showed normal renal

function. There were no urinary casts. The boy was given calciferol, 4 minims twice daily, and calcium gluconate, 100 grains three times a day, by mouth, without any clinical or radiological improvement ; he has continued to take these over a period of nearly three years, during which time he has had in addition three courses of intramuscular vitamin D, each course consisting of four injections of 500,000 units at weekly intervals. He has also had ultra-violet light therapy. He has grown only $3\frac{1}{2}$ inches in this time, the figures for blood calcium, phosphorus and phosphatase remain unchanged, and finally



FIG. 2.—Case 1. May, 1936.

there is little, if any, skeletal improvement as judged by clinical and radiological appearances (fig. 3).

Case 2. F. A., a girl aged eight years (sister of J. A., case 3, and daughter of Mrs. A., case 4), was brought to the out-patient department in August 1935 on account of knock-knees which had been present since the age of four years. Feeding had been normal ; there was no history of diarrhoea and no symptoms to suggest renal disease.

ON EXAMINATION there was clinical evidence of rickets, with marked bowing of the femora and genu valgum (fig. 4). X-ray examination of the skeleton confirmed this diagnosis (fig. 5). The blood calcium and phosphorus were

both normal, whilst the phosphatase was 71 units. Calcium and phosphorus balances were normal. There was no clinical evidence of renal disease. Figures for blood urea, non-protein nitrogen and cholesterol were normal; urea concentration and urea clearance tests gave normal figures and uroselectan x-ray examination of the renal tract showed no abnormality. The total faecal fats were 27.8 per cent. with normal splitting. Fractional test meal, complete blood count and sugar tolerance curve were all normal and blood Wassermann

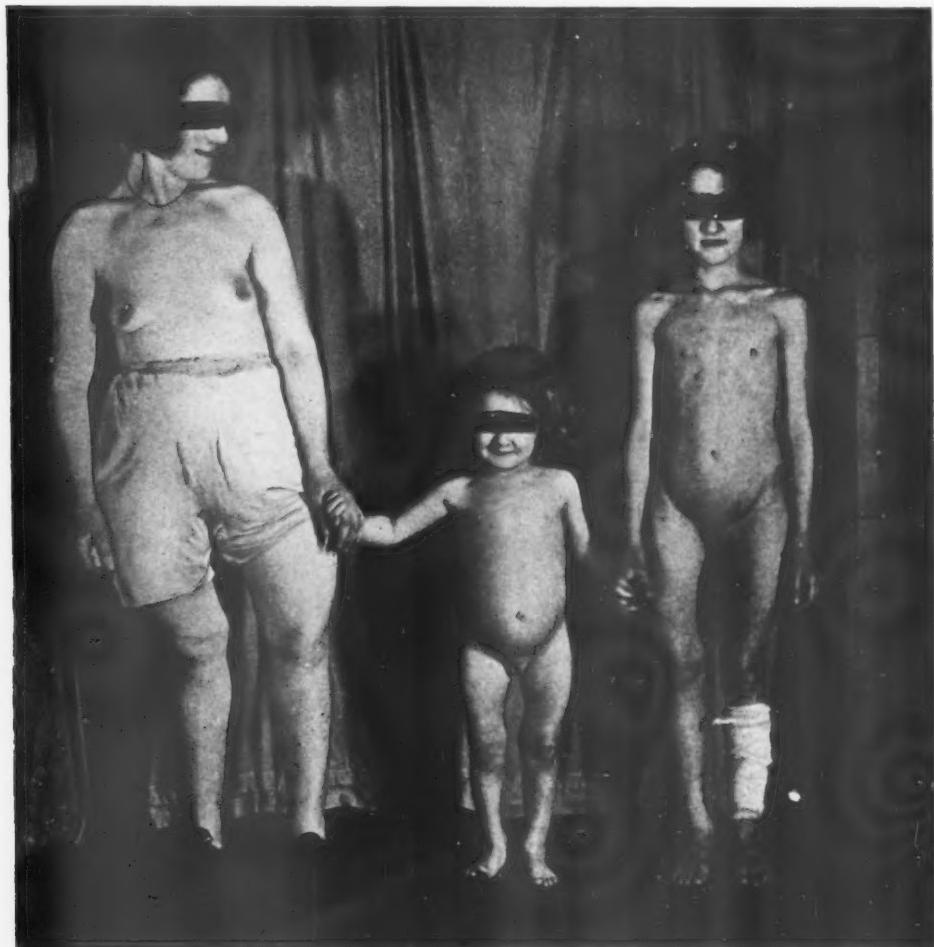


FIG. 3.—Case 1. December, 1938.

reaction was negative. Dentition was normal for her age. She was placed on calciferol, 4 minims twice a day, and calcium gluconate, 120 grains three times a day, by mouth, and in addition has received four courses of intramuscular calciferol over a period of three and a half years, each course consisting of four injections of 500,000 units given at weekly intervals. She has also had ultra-violet light therapy. Blood calcium and phosphorus remained normal, phosphatase fell to 37 units but further x-ray examination failed to reveal any skeletal improvement (fig. 6). She has, however, grown six inches while under treatment.

Case 3. J. A., a girl aged four years (sister of F. A., case 2), was brought

to the out-patient department by her mother (Mrs. A., case 4) by request for examination, and it was found that she also showed clinical evidence of rickets (fig. 4). X-ray examination of her skeleton confirmed this diagnosis (fig. 7). Blood calcium and phosphorus were normal, whilst phosphatase was 39 units. Calcium and phosphorus balances were normal. There was no history of diarrhoea, no symptoms suggestive of renal disease, and feeding had been normal. Analysis of the faecal fats gave a total of 10·9 per cent. with normal



Mrs. A.

J. A.

F. A.

FIG. 4.

splitting. No casts were present in the urine. The blood urea and Van Slyke urea clearance test were normal and uroselectan x-ray examination of the renal tract showed no abnormality. A complete blood count was normal.

She was placed on calciferol, 4 minims twice a day, and calcium gluconate, 120 grains three times a day, by mouth, and was given four courses of intra-muscular calciferol over a period of two and a half years, each course consisting of four injections, each of 500,000 units given at weekly intervals. She has also had ultra-violet light therapy. The blood calcium and phosphorus remained normal, while the phosphatase fell to 20 units and further x-ray



FIG. 5.—Case 2. August, 1935.



FIG. 6.—Case 2. December, 1938.

examination showed a tendency to healing of the rickets (fig. 8). During this time her height increased by $3\frac{1}{2}$ inches.

Case 4. Mrs. A., aged 36, brought her two daughters (F. A., case 2, and J. A., case 3) to the out-patient department as described. It was noticed that she was of small stature and on examination she presented, in addition, bowing of the femora and tibiae (fig. 4) whilst x-ray photographs of her skeleton confirmed this and presented the radiological appearances of healed rickets. She stated that her legs had become bowed at about the age of four years and she



FIG. 7.—Case 3. April, 1936.

had had osteotomies performed at the age of six. Her blood calcium, phosphorus and phosphatase were all normal. She has one other child, also a girl, now aged six who is normal and there is no evidence of rickets in any other members of the family either on the maternal or paternal side.

Commentary

At about the same time as the above cases came under observation there also presented for treatment two Indian boys. Clinically and radiologically they appeared to be suffering from the same disease, and yet there was a striking difference in their response to the same therapy. It is in order to emphasize this that the following cases are included in this paper.

Case 5. C. P., a boy aged thirteen years, brother of K. P. (case 6), attended the out-patient department in July 1936 complaining of pains in the knees on walking of some two years' duration. He had been born in India and had come to England in 1932, i.e. two years before the onset of the symptoms. He was a breast-fed baby and since then had been on a strict vegetarian diet, which, however, included plenty of unboiled milk. There was no history of diarrhoea or of any symptoms suggestive of renal disease and there were no serious illnesses in the past history. Apart from his brother, K. P., no other members of the family suffered from any bony disease.



FIG. 8.—Case 3. December, 1938.

ON EXAMINATION the boy was of normal height (fig. 9) and no abnormal physical signs were discovered on examination of the cardiovascular, respiratory or central nervous systems. The blood pressure was 105/70 mm. Hg, the optic fundi were normal, and the urine contained no abnormalities. The femora were bowed laterally, there was marked genu valgum, and the wrist epiphyses were enlarged.

The following renal investigations were performed with normal results : Van Slyke urea clearance test, estimation of blood urea and non-protein nitrogen and uroselectan x-ray of the renal tract. Estimation of the faecal fats was normal. A glucose tolerance curve, fractional test meal and complete blood count were normal. The blood calcium was 7.5 and blood phosphorus

4.1 mgm. per 100 c.c., while the blood phosphatase was 85 units. The calcium balance and phosphorus balance were normal. X-ray examination of the skeleton showed advanced rickets (fig. 10). The skull and pituitary fossa were normal.

TREATMENT. The boy was given calciferol, 4 minims twice daily and calcium gluconate, 100 grains three times a day, and showed steady improve-



FIG. 9.—Case 5.

ment both clinically and radiologically (fig. 11). The blood calcium rose to 10 mgm. per 100 c.c. and the blood phosphatase fell to 47 units.

Case 6. K. P., a boy aged eight years, attended the out-patient department in July 1936 with his brother C. P. (case 5), complaining of difficulty in walking which had been present for one year, i.e. three years after coming to England. He had been born in India, was breast fed and then had been on a strict vege-



FIG. 11.—Case 5. September, 1936.

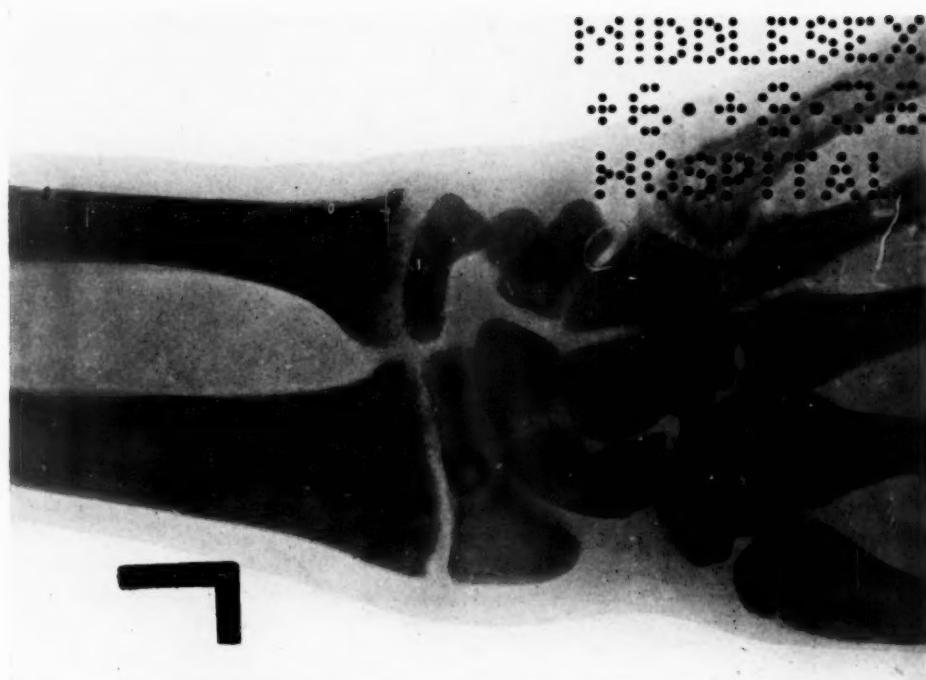
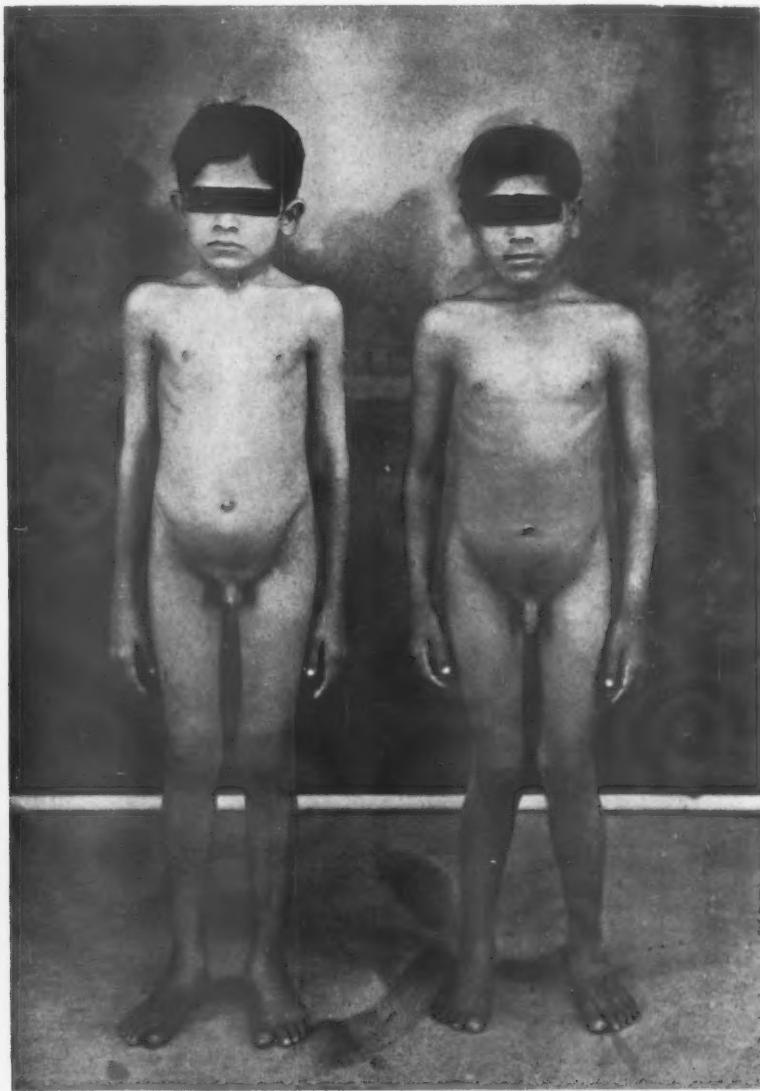


FIG. 10.—Case 5. July, 1936.

tarian diet, containing plenty of unboiled milk. There was no history of diarrhoea or any symptoms suggestive of renal disease. There were no serious illnesses in the past history.

ON EXAMINATION he was small in stature (fig. 12) and was pitted with small-pox scars. No abnormal physical signs were elicited on examination of the



Normal control.

K. P.

FIG. 12.—Case 6.

cardiovascular, respiratory or central nervous systems. The blood pressure was 100/60 mm. Hg. The optic fundi were normal and the urine contained no abnormalities. Examination of the skeletal system revealed genu valgum, femorae bowed laterally, enlarged wrist epiphyses and a rickety rosary. The following renal investigations were performed with normal results : Van Slyke urea clearance test, estimation of blood urea and non-protein nitrogen

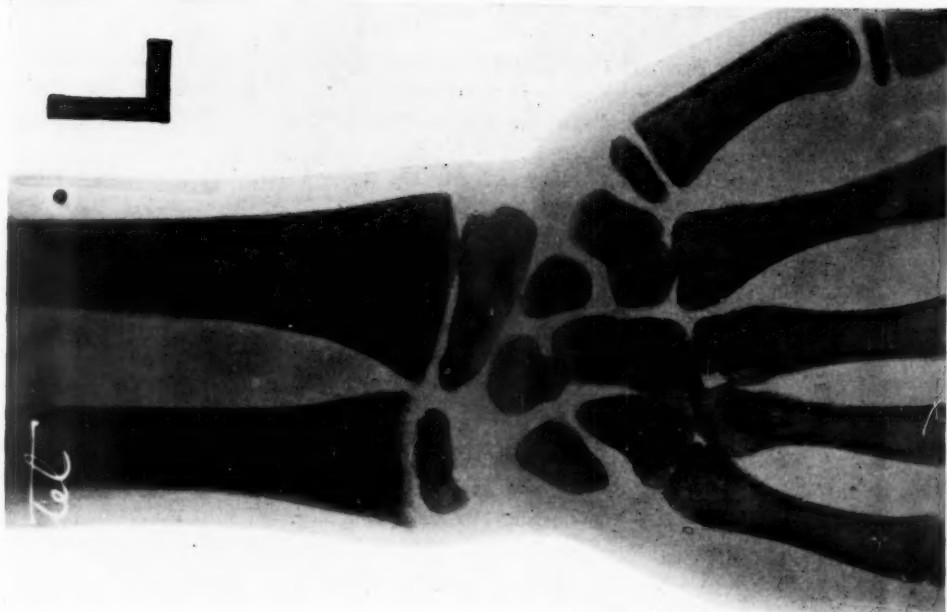


FIG. 14.—Case 6. September, 1936.



FIG. 13.—Case 6. July, 1936.

and uroselectan x-ray examination of the renal tract. Estimation of the faecal fats was normal. Sugar tolerance curve, fractional test meal and complete blood count were normal. The blood calcium was 6.2 and blood phosphorus 5.7 mgm. per 100 c.c., while the blood phosphatase was markedly increased, being 96 units. The calcium and phosphorus balances were both normal. X-ray examination of the skeleton showed advanced rickets (fig. 13). The skull and pituitary fossa were normal.

TREATMENT. The boy was given calciferol, 4 minims, twice a day, and calcium gluconate, 100 grains, three times a day, and showed steady improvement both clinically and radiologically (fig. 14). The blood calcium rose to 9.2 mgm. per 100 c.c. and the blood phosphatase fell to 52 units.

Both boys returned to India in February 1937, and their doctor has written to say that their progress has been maintained.

Discussion

It is difficult to understand the mechanism of production of these cases of vitamin-resistant rickets. There can be no reasonable doubt that they are cases of true rickets, for they are identical, clinically and radiologically, and in their lack of response to any known form of therapy, with the case described by Albright, Butler and Bloomberg (1937), similarly observed and treated over a number of years and in which biopsy gave final proof of the disease. Moncrieff (1935) has seen a similar case in a child aged seventeen months.

In nutritional rickets and in rickets due to lack of sunlight, the response to therapy is invariably rapid and striking (cf. cases 5 and 6). In coeliac disease the etiology of the rickets is fairly well understood and ultra-violet light alone causes healing of the rickets. The cases here reported showed no healing after such therapy. In advanced renal disease there is gross impairment of renal function, with a consequent profound disturbance of calcium and phosphorus metabolism and alteration of the blood figures for calcium and phosphorus. In the growing child rickets ensues, the exact mode of production being somewhat obscure. In the cases of vitamin-resistant rickets here described, not only is renal function normal, but the figures for blood calcium and phosphorus remain within normal limits. The blood phosphatase, on the other hand, is invariably high, as it always is in active rickets, giving some indication of the activity of the rachitic process.

Albright and his co-workers, in their case quoted above, investigated the possibility of calcium drain, due to hyperparathyroidism, with negative results. The normal blood calcium and calcium balance in these cases is sufficient to rule out a primary hyperparathyroid defect. A possible biochemical factor has been suggested by Hamilton and Dewar (1937) in that they found that the addition of the sodium salts of citric or tartaric acid prevented the development of rickets in rats when added to a rachitogenic diet.

Since vitamin-resistant rickets is evidently not due to nutritional disturbance, lack of sunshine, hyperparathyroidism, faulty absorption or renal impairment, and since the condition heals spontaneously when growth ceases, the fault may perhaps be a failure of utilization at the site of bone growth.

Summary

Four cases of rickets are described in none of which was there any evidence of malnutrition, lack of sunlight, calcium drain, coeliac or renal disease, and in none of which did any of the known forms of therapy, given over a period of several years, produce evidence of healing. Healing occurs spontaneously when growth ceases. It is suggested that the fault may be a failure of utilization at the site of bone growth.

Thanks are due to Dr. H. E. A. Boldero for permission to record cases 5 and 6, to Dr. Graham Hodgson for the use of the x-ray photographs, to Professor E. C. Dodds for the biochemical investigations and to Dr. J. W. Todd for the photographs of all cases except case 6, which was taken by Dr. Patel.

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CASE REPORTS

A CASE OF ARACHNODACTYLY

BY

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According to Burch (1936) the total number of cases of arachnodactyly reported in the literature up to the year 1936 was in the neighbourhood of one hundred and twenty, and from an analysis of these he concludes that as a general rule the nervous system and the mentality are not affected, the general intelligence being often especially good and consistent with the possibilities of education.

In my experience this condition is by no means rare in the feeble-minded, who, indeed, afford a happy hunting-ground for nearly all the recognized forms of skeletal deformity. In the course of the last fifteen years I have seen five cases of arachnodactyly with associated mental defect, of which the following is an interesting example.

Clinical report

G. B., a male imbecile, aged sixteen years, was admitted to Leavesden Hospital on January 17, 1920.

History.—He was the third child in a family of five; the second died of scarlet fever when nine years old; the other three children were healthy. The father was healthy, but the mother suffered from cardiac disease and had an attack of rheumatic fever some months prior to the birth of the defective. Labour was normal and the patient was born deformed. No history of skeletal disease could be obtained in the antecedents.

State on admission.—The patient was an epileptic imbecile with a mental age of five years. He was clean, tidy and a useful ward worker. Unlike most epileptics, he was docile and good-tempered. His fits were frequent and severe.

PHYSICAL EXAMINATION.—September 16, 1924. Owing to his numerous skeletal deformities the patient's appearance was most unusual (fig. 1). He was sixty inches in height, with a head of unusual contour, a narrow chest, limbs of unusual length, a general absence of subcutaneous fat and a poorly developed musculature. The head measured fifty-three cm. in circumference; breadth fourteen cm.; length eighteen cm.; cephalic index seventy-seven. The cranium was somewhat square, with a high forehead overhanging the face, prominent superciliary ridges and slight frontal bossing. The ears were large and stood out from the head in their upper halves. The nose had a sunken bridge with large, broad nostrils directed forwards and downwards. The chin

was large and the inferior maxilla presented peculiar spur-like processes projecting downwards from its angles. The eyes were rather wide apart, the palpebral fissures obliquely set, sloping downwards and outwards. The pupils were myotic and there was a bilateral correctopia, equal and opposite in the two eyes, the position being up and out. There was a slight degree of rotary nystagmus. The lids showed granules, typical of trachoma.

The upper limbs were abnormally long and thin, the elbow joints enlarged, the ulnar heads forming prominent swellings on the inner aspect of the ante-cubital fossae. Full extension of the elbows was not possible. On both sides the radius and ulna were curved antero-posteriorly and the upper third of the radius was bent inwards towards the ulna. The hands deviated to the ulnar side and the carpal joints were loose with bursae on their dorsal aspects. The



FIG. 1.—The patient shows thoracic deformity, elongated extremities, absence of hair and adipose tissue, and multiple herniae.



FIG. 2.—Photograph taken after death. The left hand of patient. Note the long and slender fingers.

metacarpal bones could be moved freely in all directions and the digits were remarkably long and slender. At the interphalangeal joints an extreme degree of flexion or extension was possible. In particular, the terminal phalanges, which were slightly hyperextended, could be bent upwards to a right angle. On each hand the minimus showed slight contracture at the first interphalangeal joint. The thumbs were double jointed. The nails were long, slender and curved from side to side (fig. 2). The lower limbs were also long, with small buttocks, poorly defined trochanters and abnormally mobile and small patellae, their transverse measurement being one and a quarter inches. But the thinness which characterized the upper limbs was not so evident in the lower ; indeed, the legs had an appearance of solidarity. The ankles and feet were broad and bent inwards in the neighbourhood of the base of the first metatarsal bone. The distal phalanges of the three outer toes were deflected towards the middle

line, and although all the toes were long they were not quite so striking as the fingers (fig. 3). The heads of the metatarsal bones were dislocated upwards on to the dorsum of the feet, and like the metacarpals could be displaced freely in all directions. Owing to the laxity of the joints of the lower limbs and the generalized hypotonia, the feet could be placed behind the patient's neck without causing him any discomfort.

The thorax was short and narrow. The sternum projected forwards with a deflection to the right and a depression at its lower end. There was considerable flattening of the chest wall, with retraction of the intercostal spaces. There was no rickety rosary. The waist was narrow ; the spine showed



FIG. 3.—Photograph taken after death showing the peculiar deformity of the feet and the excessive length of the toes.

lordosis and scoliosis. The upper central incisor teeth were large, widely spaced and inclined towards each other at their free edges ; the canines were hypoplastic. The palate was low and broad.

The neck was rather long and broad, with some enlargement of the cervical glands. Sexual development was normal, but there was no growth of hair on any part of the body except the scalp. The thyroid and lungs were normal. Examination of the heart revealed feeble sounds with a thrill and a presystolic murmur heard at the apex. The abdominal wall was lax and there were large double inguinal and umbilical herniae. By holding his breath, the patient was able to distend all three to about three times their normal size, an accomplishment which afforded him considerable pleasure. Laboratory tests were negative. A blood Wassermann reaction performed on September 29, 1924, was negative. The superficial and deep reflexes were normal.

Death from lobar pneumonia occurred on January 14, 1926. An autopsy was held twenty hours after death.

Autopsy.—In addition to frontal bossing, the calvarium showed marked thickening of its inner table, to which the dura mater was firmly adherent. The brain weighed forty-seven ounces and apart from a simple convolution pattern showed no naked eye abnormality. Both lobes of the left lung were in the stage of grey hepatization. The heart weighed seventeen ounces. The right auricle and ventricle were markedly dilated, the mitral valve segments were thickened, with a moderate degree of stenosis of the orifice. The hernial opening at the umbilicus admitted four fingers.

Discussion

The chief clinical features of arachnodactyly may be summarized as follows :

Skeletal defects.—In the majority of cases the skull is dolichocephalic with prominent supraorbital ridges, bossing of the frontal eminences, a broad and sunken nose, a narrow palatal arch and a massive chin. A certain degree of hypertelorism is not uncommon. The ears usually protrude from the head in their upper halves and show enlargement of their lobes. Usually normal, the teeth may be long and narrow, like the bones of the limbs. The face is thin and may present a prematurely old and pained expression. The limbs are excessively long and slender. Not only is there a real increase in the length of the extremities compared with that of children of the same age, but also a relative increase in comparison with the height. Thus, the extended arms may reach almost to the knees. The metacarpal bones and phalanges show a marked increase in length, the lengthening in some cases being relatively greatest in the terminal phalanges, giving to the fingers a delicate, spider-like appearance to which the condition owes its name. Roentgenograms may reveal the presence of epiphyses at the proximal and distal ends of the first and second metacarpals and all the phalanges. The feet also show an elongation due to the long and slender metatarsal bones and toes ; of the latter, the outer three often show an inward deflection of the terminal phalanges. Various thoracic deformities may be encountered. Of these 'trichterbrust' is the most common. In some cases the thorax is pigeon-breasted, and in others narrowness and flattening of the chest wall may be seen. In nearly all cases there is some degree of kyphosis or scoliosis, to which there may be added winging of the scapulae. Accompanying these skeletal changes there is nearly always a laxity of joints and ligaments, more particularly those of the elbows, fingers and knees. This may be so marked as to permit of actual subluxation. Various writers describe contractures : there may be inability to supinate, to extend fully the thighs or the fingers.

General and visceral defects.—Emphasis is laid by nearly all writers on the poorly developed musculature and the striking degree of hypotonia, which may suggest amyotonia congenita. Subcutaneous fat is often notably deficient and its absence accentuates the unnaturally long arms and legs. In a significant proportion of cases cardiac disease is present. The defect may be of a congenital nature, such as patent foramen ovale, or valvular disease acquired sub-

sequent to an attack of endocarditis. In a few cases deformities of the blood vessels have been noted. As a rule the nervous system escapes implication and the general intelligence is usually described as normal.

Ocular defects.—In recent years the association of arachnodactyly with ocular changes has received much attention from the ophthalmologist. In about one-half of all the recorded cases ectopia lentis is present. The ectopia may be seen in all positions, though an upward dislocation is the commonest. Not infrequently the subluxation is incomplete and the lenses may be smaller than normal. Opacities of varying size and density have been described. Associated with ectopia lentis there are usually iridodonesis and contracted pupils; the latter dilate feebly under the influence of a mydriatic. A myopic elongation of the eye is usually present, and myopia as much as forty to sixty diopters has been recorded. Hypermetropia is rare.

On comparing the clinical features of a typical case of arachnodactyly with those found in the case recorded above, it will be seen that in the latter the majority of the cardinal signs were present. The presence of frontal bossing, prominent supraorbital ridges, sunken nose, malformed ears, massive chin, abnormally long hands and feet, thoracic and spinal deformities, cardiac disease and an extreme degree of muscular hypotonia left no room for doubt in the diagnosis. It is unfortunate that as the state of the lens escaped observation, it is not known whether a displacement was present, but the presence of bilateral correctopia, which is known frequently to accompany ectopia lentis, suggests that the employment of a mydriatic might have revealed this malformation. In certain features the appearance of the patient was suggestive of rickets, but no history of this condition was forthcoming. Unquestionably in its thoracic and spinal deformities and general laxity of ligaments and muscles arachnodactyly bears a superficial resemblance to rickets, but there appears to be no evidence for believing that rickets plays any part in the etiology of this condition.

Several features presented by the patient were not typical of arachnodactyly. According to Young (1929) in sixty-five per cent. of cases dolichocephaly is present; in the case here presented a cephalic index of seventy-seven indicated a mesocephalic type of head. The spur-like processes attached to the angles of the lower jaw, the marked enlargement of the elbow joints and the small patellae were unusual findings, and the presence of three large herniae which the patient could inflate at will were exceptional and no doubt an indication of the general lack of tone and poor development in the musculature of the body.

Various writers have suggested a causal relationship between the multiple deformities of arachnodactyly and modifications of the ductless glands, and in this connexion it is of some interest to note that although sexual development was normal, there was no growth of hair on the patient's face, trunk and limbs. Arachnodactyly, which can be both familial and hereditary, would appear to be a dystrophy in which there is a disturbance in the growth of mesoblastic tissues. The suspensory ligament of the lens is probably of ectodermal origin, and if a defect of this ligament is concerned in the production of ectopia lentis, then some explanation other than a fault in the mesodermal anlage must be found. In

the absence of histological evidence several theories have been suggested. Zentmayer (1936), for example, points out that the lens may owe its displacement to a rupture of the zonular fibres, such rupture being itself secondary to a myopic stretching of the coats of the eye. Another explanation, quoted by Zentmayer, rests on the assumption made by Collins and Hess that luxation can occur when the adhesions between the ciliary body and the margins of the lens are denser and less elastic on one side than on the other.

Another and broader conception places ectopia lentis with its associated skeletal defects in the category status dysraphicus. Originally defined by Bremer (1926), the characteristics of this condition are referable to a disturbance in the embryonal closing of the primitive central spinal canal. The range of disorders which may follow from this interference is wide and varies according to the degree of damage sustained by the cells of the medullary tube. In addition to a disproportion between the height and the span-measurement, the horizontally extended upper limbs exceeding the height of the patient, there may occur syringomyelia, spina bifida occulta, funnel-shaped chest, deformities of the fingers, muscular atony, acrocyanosis and anomalies of the mammary glands, the latter sometimes being associated with dislocation of the lens, Horner's syndrome and heterochromia iridis.

These defects are said to behave as Mendelian traits, and whilst this may also be true of ectopia lentis, the genetic factors underlying arachnodactyly are still in dispute and require further investigation, though there is certainly evidence for the view that the two conditions are linked by inheritance.

Summary

A case of arachnodactyly in an epileptic male imbecile is described. Among unusual features present were a mesocephalic cranium, spur-like processes attached to the angles of the inferior maxilla, enlargement of the elbow joints, small patellae, multiple herniae and an absence of hair on all parts of the body except the scalp.

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A CASE OF MORQUIO'S DISEASE

BY

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In 1929 Morquio of Montevideo described two children, brother and sister, with curious skeletal deformities. To this he added in 1935 the description of two other children of the same family with similar deformities. Since 1929 reports of nine families have appeared in each of which two or more children have been affected in the same way (Ruggles, 1931; Barnett, 1933; Coward and Nemir, 1933; Davis and Currier, 1934; Valentin, 1930; Brown, 1933; Giraud and Bert, 1935; Summerfeldt and Brown, 1936). In addition six non-familial cases have been reported by Ruggles (1931), Meyer and Brenneman (1932), Sainz de los Terreros (1934), Freeman (1938) and Guerin and Lachapèle (1938).

The condition has been generally accepted as a disease sui generis and as only thirty cases have been recorded—only six of them non-familial—it has been thought worth while to add a report of another isolated case.

Case Report

The patient, a boy nine years of age, was brought to hospital because of a leg injury. This proved to be of quite a trivial nature and he was admitted to medical wards for investigation of the obvious skeletal deformity which he presented.

Family history.—No consanguinity of the parents can be traced. The patient's mother is a small woman (height 4 feet 9 inches), but she appears to be well proportioned and there is no evidence of skeletal deformity. The boy is the sixth in a family of eight children, of whom three have died (from a birth injury, a burn, and meningitis respectively); another suffers from epileptic fits. None of the family has been dwarfed or deformed in any way.

Patient's history.—The child was born at full time by an instrumental delivery. At birth he appeared normal and weighed eight pounds. He was breast fed for four months but subsequently was bottle fed till the age of fifteen months when mixed feeding was instituted. No additional vitamin or mineral preparations were given.

The first teeth were cut at the age of eleven months and talking began at one year. Walking was beginning at the age of one year and nine months when he was operated on for an inguinal hernia. Shortly after this he fell and fractured his left leg, and further attempts at walking were delayed until he was two-and-a-half years old. Additional leg fractures occurred at four years, six

years and seven years of age, all necessitating long periods in bed, and the injury with which he was finally seen proved on x-ray examination to be yet another fracture of the leg which in this instance was only partial.

His walking is still slow and unsteady and he falls frequently. From the time he first began to walk his back has been noticed to be growing increasingly curved. His behaviour has always been normal.

General examination.—The boy's general appearance is illustrated in fig. 1 and fig. 2, and his measurements and weight are compared with normal values for a boy nine years of age in table 1.



FIG. 1.—Lateral view of the patient.



FIG. 2.—The patient with a normal boy of the same age.

TABLE 1

	PATIENT	NORMAL
Weight ..	18.6 kgm.	26.6 kgm.
Height ..	103 cm.	127 cm.
Head circumference ..	53 cm.	53 cm.
Chest circumference ..	60 cm.	64 cm.
Sitting height ..	58 cm.	72 cm.
Upper limb length ..	47 cm.	55 cm.
Lower limb length ..	49 cm.	64 cm.

From this it will be seen that the stunting of growth involves the lower limbs and the trunk to an approximately equal extent.

The most striking abnormalities are in the spine and the thorax. The spine shows a severe though gradual kyphosis affecting the dorsal and upper lumbar regions. This deformity is quite fixed and no spinal movements of these parts are possible. Cervical movements are present but limited. The thorax displays a marked pigeon-breast deformity ; the sternum is pushed forward and the antero-posterior diameter of the chest is greatly increased while its lateral diameter is diminished. There is no beading of the ribs or other evidence of rickets. The lower costal margins descend to the iliac crests and the relatively long arms bring the finger-tips almost down to the level of the knees. The general appearance is reminiscent of a case of Paget's disease in miniature. In the standing position there is seen to be knock-knee and flat-foot. These deformities are not due to bony changes but to abnormal mobility of the joints, occasioned by laxity of the ligaments. The gait is characteristic ; he walks on a broad base with his trunk bent forward. His head is carried as far back as he can get it and his arms are also held back in an attempt to keep his centre of gravity over his feet. There is a pronounced waddle—*'comme un canard'* (Morquio, 1929)—and his progress is slow and uncertain, with a strong tendency to fall forward. The head appears to be of normal form and size.

There is obvious enlargement of the joints, especially at the knees and elbows. Joint movements are, however, quite free and in some places there is even abnormal mobility due to laxity of the ligaments. Joint crepitus can be detected in both the shoulder and the elbow joints. There is some limitation of upward movements of the arms due apparently to overgrowth of the acromion processes. General muscular development and tone are poor, but this may be due to the prolonged confinement to bed.

The genitalia appear large for a boy of nine years—a feature noted by Morquio (case 1, 1935)—and priapism is a frequent occurrence.

Routine examination of respiratory, alimentary, cardiovascular, renal and nervous systems reveals no abnormality. On ophthalmoscopic examination the fundi appear to be normal. The urine contains no abnormal constituents and the Wassermann reaction of the blood is negative.

The intelligence quotient (kindly estimated by Dr. V. J. M. Stark) is eighty-eight per cent.

Radiological appearances (fig. 3 to 6).—Skiagrams show an apparently normal development of the shafts of the long bones except for a severe degree of osteoporosis. At the epiphyses and metaphyses, however, an abnormal condition is seen ; in some regions, notably the lower ends of the humeri, there is excessive epiphyseal growth with the formation of osteophytes, while at other situations (e.g. the carpus and the upper ends of the femora) ossification is delayed and distorted. Clear islets of cartilage, separated by irregular bony strands, can be seen persisting throughout the substance of the epiphyses. At the upper ends of the femora the formation of the heads and trochanters is defective ; whilst the carpus, though showing the normal number of ossifying centres, is poorly developed for a boy nine years of age. Skiagrams of a lateral view of the spine show that the vertebral bodies are flattened vertically, a condition which has been described as 'biscuit shaped' and to which the term 'platyspondyly' has been applied. The intervertebral discs are as wide as or wider than the neighbouring vertebral bodies. In an antero-posterior view the epiphyses forming the lateral and articular processes are seen to be irregularly formed and it is presumably the interlocking of these processes which accounts for the immobility of the spine. Skiagrams of the skull show no abnormality.

Biochemical findings.—During the boy's stay in hospital the following estimations were made. Serum calcium 12.1 mgm. per cent. ; inorganic blood phosphorus 3.8 mgm. per cent. ; plasma phosphatase 18.8 units (maximum normal 12 units) ; blood non-protein nitrogen 40 mgm. per cent. ; standard



FIG. 3.—Skiagram of arm and hand showing irregularity of metaphysis and epiphyses, delayed ossification and osteophytes.

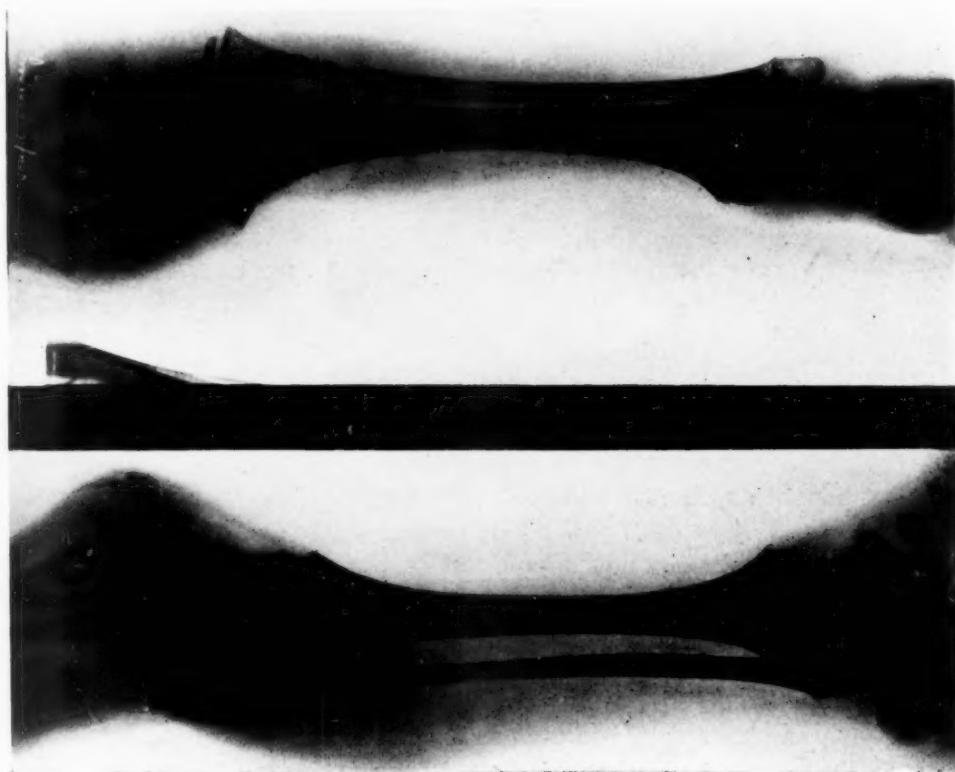


FIG. 4.—Skiagram of knee and ankle joints showing osteoporosis, osteophyte formation and irregular ossification.

urea clearance 90 per cent. ; urea concentration after 15 gm. urea 3.3 per cent. ; blood cholesterol 105.7 mgm. per cent.

Subsequently thirty minims of adexolin (ten thousand units of vitamin D) were administered daily for one month without change in the biochemical findings. The figures at the end of that period were : serum calcium 12.4 mgm. per cent., phosphorus 3.6 mgm. per cent., and plasma phosphatase 19.0 units. Skiagrams did not show any improvement in the osteoporosis or in the other bony abnormalities.



FIG. 5.—Skiagram of pelvis and hip joints showing defective epiphyseal formation at upper ends of femora.

Discussion

The general appearance and the radiological findings of the boy resemble those described by Morquio and others so closely that there is little doubt that he is an example of Morquio's disease ; bone, joint and postural changes show a striking resemblance to the illustrations in Morquio's publications. Morquio's disease may readily be distinguished from other types of dwarfism such as achondroplasia, gargoyleism and late rickets by the general aspect of the patient and the bony changes as shown by radiography. Consanguinity of the parents, so strongly emphasized by Morquio as a possible aetiological factor, was not present in this case and indeed has been noted in none but the original family which Morquio described. In Morquio's first two cases (1929) low values were found for the serum calcium (5.2 and 4.5 mgm. per cent.) but in the two cases

he described later and in those reported by subsequent authors normal values were found. In the present case, though the serum calcium and phosphorus



FIG. 6.—Skiagram of lateral view of spine showing flattened wedge-shaped vertebrae with widened intervertebral spaces—platyspondyly.

values were normal, the plasma phosphatase was increased to 19 units (maximum normal 12 units) and this value persisted in spite of heavy dosage with vitamin D. Phosphatase estimations have been made in only two previous cases of

Morquio's disease (Summerfeldt and Brown, 1936). The values found were 12.6 and 19.2 units but the authors make no comment beyond the statement that the biochemical findings were all within normal limits. The patients of Summerfeldt and Brown showed a positive calcium balance on one grammie of calcium daily but a negative balance on one-tenth of a grammie daily. In the present case no estimation of calcium retention was made.

There are only two other conditions, Paget's disease of bone and healing fractures, in which a raised plasma phosphatase value is found in conjunction with normal levels of the serum calcium and phosphorus. Although the general resemblance of the patient to a case of Paget's disease already mentioned, raises the possibility that Morquio's disease may be a juvenile form of Paget's disease, radiological evidence lends no support to this attractive speculation.

The present case presents one feature noted in none of the previously recorded cases, the occurrence of pathological fractures during the first few years of life. This is, no doubt, an expression of the osteoporotic condition present.

The prognosis in Morquio's disease is as yet unknown. Morquio's oldest patient was nineteen years of age when reported in 1935. Though grossly deformed and crippled, in other respects he was well both mentally and physically. As the other recorded cases are too young to draw any conclusions regarding the outcome of the disease the prognosis must remain in doubt.

No effective treatment has been discovered. Ruggles (1931) found thyroid and pituitary extracts to be of no value and in the present case, as in the one reported by Meyer and Brenneman (1932), vitamin D preparations caused no improvement. In Barnett's case (1933) osteotomy resulted in some improvement in walking. Bone removed at the operation was histologically normal.

No post-mortem examination has as yet been reported in a case of Morquio's disease.

Summary

An isolated (non-familial) case of Morquio's disease in a boy first seen at the age of nine years is described. Walking began at one year and nine months and its onset was followed by a series of pathological fractures (a feature not previously noted in Morquio's disease). Increasing kyphosis and thoracic deformity developed and the gait remained unsteady.

Skiagrams show generalized osteoporosis, marked platyspondyly, and great irregularity of epiphyseal growth. The skull is not affected and mentality is normal.

There is increase in the amount of plasma phosphatase in association with normal values for the serum calcium and phosphorus. The phosphatase and the radiological appearances were uninfluenced by the administration of large doses of vitamin D.

Thanks are due to Professor G. B. Fleming for permission to publish this case and for his help in the preparation of this paper, and to the staffs of the biochemical and radiological departments of the hospital for their aid in the

investigations. Thanks are also due to the Medical Research Council for defraying part of the expenses.

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BESNIER-BÖECK'S DISEASE IN AN INFANT

BY

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Besnier-Böeck's disease usually affects young adults, but may occur at any age. It is rare in children, and is met with only exceptionally in infancy. The case reported here is therefore of considerable interest.

Besnier (1889) described a syndrome characterized by bluish-red or violet infiltrations of the skin of the fingers, toes, cheeks, and nose. It bore some resemblance to the ordinary chilblain and was called by him *lupus pernio*. Böeck (1899) reported several cases having red or bluish coloured infiltrations of the skin, and enlargement of lymph glands. To this syndrome he gave the name of benign sarcoid of the skin. He came to believe that the lesions were inflammatory in nature and probably tuberculous. He later renamed the disease *benign miliary lupoid*. Schaumann (1924) put forward the view that Böeck's sarcoid was merely part of a general disease affecting many other organs besides the skin. He showed that Böeck's sarcoid and *lupus pernio* were identical histologically, the lesion being an area of cellular infiltration consisting of endothelial cells, some lymphocytes and a variable number of multi-nuclear giant cells. There was, however, never any caseation as in tuberculosis. Later a progressive fibrosis usually took place. He emphasized the visceral localization of the disease and described lesions in the lungs, and lymphatic tissues. He shared Böeck's opinion that the disease was a form of tuberculosis. Jungling (1921) described under the name *osteitis tuberculosa multiplex cystica* curious cystic spaces in the bones of the hands and feet of patients who suffered from sarcoid. Other bones may also be affected.

A voluminous literature has gathered round this interesting malady. Hunter (1936) has given an historical account of the earlier papers written about it, and Volk (1931) has recorded a full description of the skin lesions. A complete account of the syndrome together with a report of eight cases is to be found in the paper by Longcope and Pierson (1937). In Snapper's (1938) beautifully illustrated monograph, which was recently published, thirteen more cases are reported.

Case report *

Bernard, C., a male aged two years, was first seen in January, 1938, at the Hospital for Sick Children, Great Ormond Street. For three months he had had painless swellings of the fingers of both hands. He was a ten weeks premature infant, born of unrelated parents ; his birth weight was 4½ lb. His parents were healthy. There are four other children, all normal. There was no history of tuberculous contact.

On examination, the boy was pale. His weight was 24 lb. Both eyes were slightly prominent. The respiratory and cardio-vascular systems were normal. The blood pressure was 115/80 mm. Hg. The spleen and liver were not palpable. The lymph glands were not enlarged. There was a fusiform enlargement of all the fingers of both hands (fig. 1). The skin was shiny and slightly reddened.



Fig. 1.—The photograph shows the sausage-shaped swelling of the fingers and the shiny skin.

The toes were normal. There were no other skin lesions. The optic fundi were normal and the media were clear. The patient was afebrile while he was in hospital.

Investigations :

BLOOD COUNT : Red blood cells, 4,560,000 per c.mm. ; Haemoglobin, 62 per cent. ; Colour index, 0·7 ; White blood cells, 7,000 per c.mm. ; Polys., 44 per cent. ; Lymphos., 51 per cent. ; Monos., 2 per cent. ; Eosinos., 2 per cent. ; Basophils, 1 per cent.

WASSERMANN REACTION : Mother and Child—Negative.

MANTOUX REACTION : 1 in 1,000 to 1 in 10—Negative.

* This case was shown at the Children's Section of the Royal Society of Medicine on March 25, 1938, see *Proc. roy. Soc. Med.* 1938, 31, 1124. The Honorary Editors have kindly granted permission to publish it here.

PLASMA PROTEINS : Fibrin, 0.34 gm. per cent.; Albumin, 4.0 gm. per cent.; Globulin, 1.54 gm. per cent.; Total proteins, 5.88 gm. per cent.

SERUM CALCIUM : 10.2 mgm. per cent.

INORGANIC BLOOD PHOSPHORUS : 4.6 mgm. per cent.

PLASMA PHOSPHATASE : 8 units.

ERYTHROCYTE SEDIMENTATION RATE : 15 mm. in 1 hour.

X-rays :

HANDS : There were multiple small cystic spaces in the phalanges of both hands. The changes were most extensive in the third and fourth fingers of the right hand and the second and third of the left (see fig. 2). The metacarpals were unaffected.

FEET : No changes in the phalanges and metatarsals.

CHEST : The lungs were normal. There was no increase in the mediastinal shadow.

LONG BONES AND SKULL : Normal.



Fig. 2.—The small cyst-like spaces are best seen in the phalanges of the second and third fingers of the right hand and the first and second of the left hand.

Course : In July, 1938, there was no change either locally in the hands or in the patient's general condition. No further lesions had appeared. A piece of soft tissue was removed from one of the affected phalanges and was examined histologically.

Histological examination (Dr. D. N. Nabarro) (see fig. 3 and 4).

The section is composed of fibrous tissue in which there are small cellular areas consisting of lymphocytes and endothelial cells. There are also several giant cells with many nuclei arranged roughly around the periphery of the cell. They resemble but are not identical with those met with in tuberculous gran-

ulation tissue. There is no caseation. No tubercle bacilli could be found in Ziehl-Nielsen stained preparations. In slides stained with methylene blue,

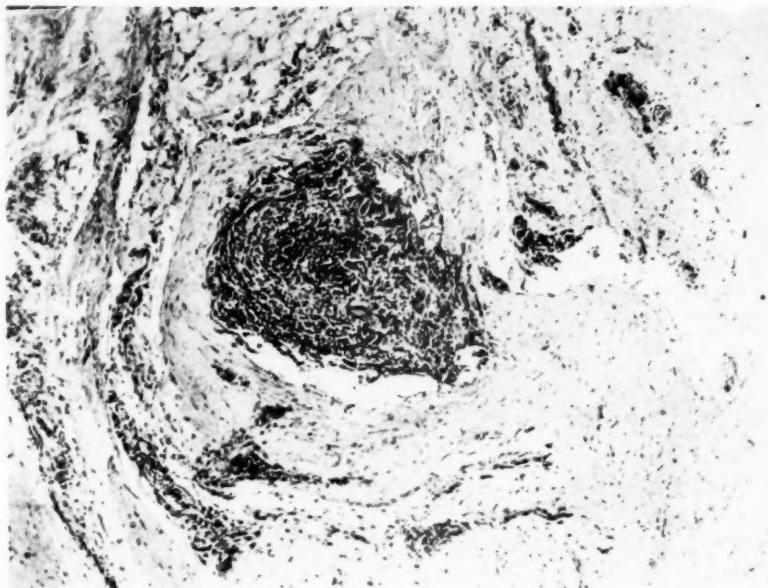


FIG. 3.—Photomicrograph showing the area of cellular infiltration amongst the mass of fibrous tissue. Several giant cells are discernible. $\times 40$.

clusters of small coccoid bodies were observed. They were situated both intra- and extra-cellularly. There was no inflammatory reaction around them. It is

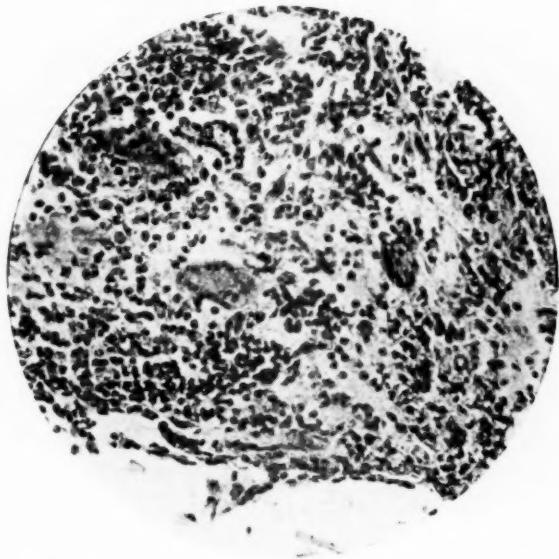


FIG. 4.—High-power view ($\times 200$) of the same section showing several giant cells.

possible that they were granules extruded from mast cells. A piece of the tissue was inoculated into a guinea-pig. No evidence of tuberculosis was found when the animal was killed eleven weeks later.

Discussion

The usual age of onset is in early adult life, between the ages of twenty and thirty years. An onset in childhood is rare.

Roos (1937) describes a case in a girl aged four years, who had lesions in the skin, liver, spleen, kidneys, lymph nodes and brain. He quotes from the literature nine other undoubted cases in children. All but two were over six years of age; one was one and a half years old and another only four months of age. All of these patients had skin lesions; five had cystic changes in the bones; two had enlargement of lymph nodes, and in two others there was enlargement of the mediastinal lymph glands. Stalmann's patient (1933) was only one and a half years of age and had lesions in the hands which closely resembled those in the case described here. There were spindle-shaped swellings of the fingers and the skiagram showed multiple cystic spaces in the phalanges. Müller (1938) reports a case in a twelve-year-old girl. She had generalized swelling of the lymph glands, diffuse lesions in the lungs and early ones in the phalanges. There was a typical histological picture. Naumann (1938) describes two cases, one in an infant of three months and a second in a child aged fourteen years. In the latter there were diffuse lesions in the lung as shown by x-ray. In both the Mantoux reaction was negative.

It is now recognized that skin lesions are found in little more than half the cases of Böeck's sarcoid. There is a well-defined group in which the deposits are found only in the viscera and glands. In some the bones only are affected. The present case belongs to this latter group. Other manifestations of the disease may appear in the course of time.

The etiology of the disease has been the subject of much discussion. Böeck, Schaumann and others believed it to be a manifestation of tuberculosis. Many investigators, however, declare that tubercle bacilli cannot be demonstrated in the affected tissues either histologically or by guinea-pig inoculation. Moreover, it is a characteristic of the lesions that they do not, as in tuberculosis, proceed to caseation. The present case lends support to the non-tuberculous theory of origin. The Mantoux reaction was negative to low dilutions of tuberculin, no tubercle bacilli were seen in the sections, and inoculation into a guinea-pig did not give rise to any tuberculous lesions. Longcope and Pierson, Snapper, and other recent writers hold the view that Böeck's sarcoid is a specific reaction of the tissues of the body to an unknown virus.

Summary

A case of Böeck's sarcoid in a boy aged two years is described. There were characteristic cystic spaces in the x-ray picture of the phalanges and spindle-shaped swellings of the fingers. A piece of tissue removed from a finger showed a typical histological picture. The incidence of the disease in children is discussed.

Thanks are due to Dr. D. Paterson and Dr. W. G. Wyllie for permission to publish this case, and also to Dr. Herbert Levy and Dr. Parkes Weber for their help with references and to Mr. Deryk Martin who took all the photographs.

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A MEDULLOBLASTOMA IN AN INFANT WITH ABNORMAL CELLS IN THE CEREBROSPINAL FLUID

BY

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This case of an intracranial tumour in an infant is thought to be worthy of record because, in spite of symptoms suggesting meningitis, a correct diagnosis was made possible by the unusual characters of the cerebrospinal fluid.

Clinical Record

C. H., a male child aged one year and nine months was brought to hospital with a left-sided facial paralysis which had developed suddenly five days previously. He seemed quite well in himself and did not appear to be in any pain. On examination it was found that the drum of the left ear was of pink colour and showed an attic bulge. The drum was incised, but pus was not obtained. The right ear was normal. He appeared to remain quite well until thirteen days later, when he became restless and irritable with a low, whining cry. Both ears at this time looked normal and he was admitted to the ward for observation.

General examination revealed a miserable infant. He was restless, waved his arms about continually, threw his head backward and forward and took no interest in his surroundings.

Physical examination elicited a positive Kernig's sign and some definite head retraction. The facial palsy was infranuclear in type. There were no apparent lesions of the other cranial nerves and all reflexes were obtained. There was a leucocytosis of 17,500 cells per c.mm., but there was no pronounced increase in the number of polymorphonuclear cells. The Wassermann reaction in the blood was negative.

Three specimens of cerebrospinal fluid were obtained by lumbar puncture at intervals of four days. The fluid was never under marked pressure. These three specimens were similar in character. The fluids were slightly turbid and deposited a small amount of bright blood. A small soft grey clot developed in the fluids after a short interval. The number of cells in the fluids averaged 430 per c.mm. These cells were quite unlike those associated with meningeal inflammation. Many of them were considerably larger and most of them were more refractile. The characters of the cells were best observed in the counting chamber, for many were disintegrated by the centrifuge in the preparation of films. The predominant cell was large and round, with a well-defined eccentric nucleus and clear protoplasm. Other cells with an obscured nucleus were filled with dark granules, whilst others had lost their outlines and were markedly degenerate. Occasionally these cells were met with in small clumps, but no clump contained more than six cells. These abnormal cells constituted more

than 90 per cent. of the whole number. Such other cells as were present were polymorphonuclear cells and lymphocytes that probably came from the blood in the fluids. The fluid protein was much increased, the chloride content was normal. Tubercle bacilli and other organisms were not identified in films and cultures proved sterile.

Twenty-one days after the onset of the facial paralysis the temperature, which had been normal, rose to 103° F. and continued high for four days. Nothing, at first, could be found to account for this temperature, but he later developed an otitis media in the right ear. After myringotomy the temperature gradually returned to the normal. At this stage he developed a left-sided hemiplegia. Neither the left arm nor the left leg was moving, the cremasteric reflex was present on the right side, but not on the left, and a positive Kernig's sign present on the right side was unobtainable on the left side. This hemiplegia proved to be transient and disappeared within five days leaving no residual paralysis.

The child became worse, was still irritable and had photophobia and marked head retraction. At no time, however, did vomiting become a symptom and no papilloedema was ever detected. The child became comatose and died exactly five weeks after the onset of his disease.

At the post-mortem examination a soft and heavy brain was found and over the base of the brain there was an extensive tumour growth. It was a dirty-grey colour, soft and friable. It extended from the cerebellum posteriorly to the frontal lobes in front. The largest mass of growth was found in the pons and cerebral peduncles. It entirely obliterated their structure and by extension upwards had forced up the floor of the third ventricle, reducing its cavity to a mere slit. The growth extensively infiltrated the more superficial portions of the cerebellum and was present in the posterior part of the fourth ventricle as a soft, cauliflower-like mass. On the under-surface of the cerebellum the tumour growth looked like a superficial grey plaque. Anteriorly it entirely obliterated the optic chiasma and passed forward along the optic nerves and the olfactory tracts. In the frontal lobes adjacent to the olfactory tracts were found two discrete tumour nodules, one in each cerebral hemisphere. The lateral ventricles were dilated and contained a great excess of fluid. This dilatation was thought to be due to the partial closure of the third ventricle, for the fourth ventricle was not markedly dilated. The growth invaded the sub-arachnoid spaces and was present along the cranial nerves in their intracranial course as a soft, grey and ragged sheath. A small amount of pus was found in the right middle ear : the left ear was clean. Histologically the growth was found to be a typical medulloblastoma.

Comment

The clinical features of this case were puzzling until the correct diagnosis of the child's condition was established by the examination of the cerebrospinal fluid. The objective signs of meningitis—head retraction, Kernig's sign, restlessness and facial paralysis—were complicated by an irregular pyrexia due to a concurrent otitis media. The clinical picture was that of meningitis, but the cells of the cerebrospinal fluid were wholly different from those associated with inflammatory disease. They could at once be recognized in the counting chamber as quite abnormal by their large size, granularity and other histological characters.

Abnormal cells like these have previously been described in the fluid in cases of medulloblastoma, but they are distinctly uncommon. Ford (1937) mentions

the case of an infant with symptoms very similar to those now described in which tumour cells were found in the fluid, while Merritt and Fremont-Smith (1937) write of their occurrence in the cerebrospinal fluid as a matter of 'great rarity.' These observers, however, seem to note such cells as affording confirmatory evidence of the presence of a tumour already diagnosed as such on clinical grounds. In the present case these abnormal cells were the only significant factors in the satisfactory solution of an interesting clinical problem. The appearances of the brain at autopsy account, in some measure, for the resemblance of the clinical picture to that of meningitis. In a fatal case of acute basal meningitis in infancy the base of the brain from the medulla forward is found clothed with pus and there is often an associated dilatation of the ventricles. In this child's brain there was no pus, but there was, instead, a rapidly growing soft tumour mass of almost identical distribution with considerable dilatation of the lateral ventricles. The sub-arachnoid spaces were filled with growth and the meningeal irritation was of neoplastic origin. This child was too young to complain of headache, but it is of interest that other signs of intracranial tumour, such as vomiting and papilloedema, were never, at any time, a feature of the disease. Ford notes the absence of papilloedema in about one quarter of the cases of medulloblastoma in infancy that have so far been described.

Thanks are due to Dr. Reginald Miller for permission to record this case.

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TEMPORARY HEMIPLEGIA FOLLOWING SYMPTOMATIC CONVULSIONS

BY

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The possibility that temporary hemiplegia may follow symptomatic convulsions receives scant notice—and sometimes no mention—even in the larger works on paediatrics. Two recent personal cases are therefore being recorded.

Case 1, P.B., a well-nourished female child, eleven months old, hitherto healthy, who had been weaned at nine months, was admitted at 7 p.m. on September 16, 1937. She had become flushed and ill six hours previously. Just before admission she became unconscious, and jerking movements of her left side were seen. On admission she was cyanosed, in coma, with clonic movements of the left arm and leg, and spasticity of the left side. Her temperature was 99.2° F., pulse rate 160, and respirations 38 per minute. Nothing else abnormal was found. Four hours later she was bright mentally, but there was complete paralysis of the left arm, face and leg. The following morning there was no longer any paralysis, but she showed definite weakness of the left arm and leg. By September 21 the leg had fully recovered, but some hypotonia persisted in her arm. One week after admission, power had fully returned. On September 17 cerebro-spinal fluid examination for cells, protein, and organisms showed no abnormality. The fluid was not under pressure. On September 18 there appeared a transient widespread pink macular rash and the child was irritable. The rash recurred for short intervals during the two following days. The throat was normal. A temperature of 99°–100° F. with tachycardia had persisted from the time of admission. On September 23 pus cells and *B. coli* were abundant in a catheter specimen of urine. The pyelitis was treated with alkalies followed by mandelic acid, and the child quickly recovered.

Case 2, R.W., a thin pale boy four and a half years old, had had measles and whooping cough when aged three years. Eighteen months before admission he had a convulsion from which there was complete recovery in two hours. There were no sequelae. One and a half hours before admission on August 27, 1938, he went into convulsive coma, and remained stuporose until brought to hospital. Examination on admission showed continued stupor, with complete paralysis of the right face and arm and weakness of the right leg. The throat appeared normal. The temperature was 99° F., pulse rate 128 and respirations 26 per minute. The paralysis was present three hours later, but not six hours later nor subsequently. Lumbar puncture was not done. The next day the temperature rose to 99.8° F., the tonsils were enlarged and studded with follicles, and haemolytic streptococci were grown from the throat. The throat was treated and recovery followed.

Comment

Transient paralyses are well known after the convulsions of idiopathic epilepsy. But it is worth considering that hemiplegia following symptomatic convulsions may be temporary, and not be of bad prognosis as regards the underlying disease. The convulsions in the above cases were not prolonged. This contrasts with the hemiplegia seen in apparently healthy children as a sequel to the sudden occurrence of a series of severe convulsions over a period of several days to a week (Pearson and Wyllie, 1935).

The conception of meningism might be usefully supplemented by that of 'encephalism,' a term which could be used to include symptomatic convulsions and their transient sequelae.

Summary

Two children are described, one with *B. coli* pyelitis and the other with acute tonsillitis, in whom the early symptoms were convulsions followed by temporary hemiplegias. Both children made good recoveries.

Thanks are due to Sir F. Menzies, Medical Officer of Health, London County Council, and Dr. D. S. Sandiland, Medical Superintendent, for permission to publish this report.

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BILIARY CIRRHOSIS

BY

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Hepatic cirrhosis is conventionally classified, on a clinical basis, as syphilitic, portal, and biliary. On a pathological basis these types are described respectively as pericellular, multilobular and unilobular. Despite subdivision into further types the clinical classification is useful and valid. This is less true of the pathological terms used to describe the three varieties.

In congenital syphilis the fibrosis is diffuse throughout the liver and the term 'pericellular' cirrhosis is a correct description. In portal cirrhosis the islands of surviving liver tissue have lost their normal structure. They are not collections of well-defined lobules, and the condition is one of cirrhosis with nodular hyperplasia rather than multilobular cirrhosis. Biliary cirrhosis has received much attention since Hanot described it in 1876. Some authors have been sceptical of its existence, except as a consequence of obstruction of the common bile duct (Hutchison, 1936), whilst the pathological description of the fibrosis as unilobular has been criticized. Three of the cases reported here are examples of biliary cirrhosis, two of them with nodular hyperplasia. The fourth is an example of pure unilobular fibrosis with the clinical picture of portal cirrhosis.

As the pathology is uncertain, it is better to use a definition of biliary cirrhosis which rests upon clinical observation. Broadly speaking, the disease is a chronic affection of the liver, not caused by syphilis, in which jaundice occurs as an early sign, and is a prominent feature throughout the course, while evidence of portal obstruction appears late or not at all. Such a definition includes cases of chronic obstruction of the common bile duct with hepatic damage, and it is convenient to consider obstructive biliary cirrhosis first.

Acquired obstructive biliary cirrhosis

In animal experiments Rous and Larimore (1920) showed that occlusion of the common bile duct leads to dilatation of the ducts behind the obstruction. The rise of pressure in the intrahepatic ducts lessens the portal blood flow, and hepatic anoxæmia results. Some of the finer ducts may rupture—Rich (1930) describes this occurrence in man—and the escaped bile is irritant. These two factors produce pericholangitis, with proliferation of the connective tissue of Glisson's capsule and scattered necrosis. Pericholangitic, or periportal,

cirrhosis is produced, the liver is jaundiced and has a hobnailed appearance, numbers of newly-formed bile ducts appear and small patches of hypertrophied liver parenchyma are found. The human liver is better able to withstand biliary obstruction than the rabbit's, but the same sequence of events is likely to occur with any long-standing obstruction. In addition, especially in calculous cases, infection of the biliary tract may play a part.

Many varieties of obstruction have caused hepatic atrophy and fibrosis—carcinoma, gall stones (Flint, 1937) and pancreatitis (Strauss et al., 1933) are the most important. Rare lesions have been reported in children : stenosis (perhaps congenital) of the common bile duct (Braithwaite, 1934), congenital cystic dilatation of the common bile duct (Wyllie, 1925 ; Weber, 1934), secondary sarcoma of the pancreas (Crooks, 1925), a tuberculous gland in the hilum of the liver (Ford, 1901). Rolleston (1907) reported syphilitic obstruction of the ducts with syphilitic cirrhosis.

The changes in the liver, apart from jaundice, may be slight or severe. The ducts are dilated and the hepatic changes vary from 'mild central necrosis to acute atrophy, and slight periportal fibrosis to definite cirrhosis' (Flint, 1937). Ascites and splenic enlargement may occur late in the disease, but this stage should not often be reached, as operative relief of the obstruction may restore health to the patient (Strauss et al., 1933).

Congenital biliary cirrhosis and congenital obliteration of the bile ducts

Congenital obliteration of the bile ducts is usually associated with hepatic cirrhosis, but it does not follow that the cirrhosis is caused by the obstruction.

Rolleston and McNee (1929) consider that toxins pass from the placenta to the foetal liver by the umbilical vein, and also by the ductus venosus into the general circulation and back to the liver by the hepatic artery. The result is cirrhosis with descending obliterative cholangitis. Others (Holmes, 1916 ; Milne, 1912) consider that the primary fault is in the development of the bile ducts, although catarrhal changes may sometimes be important, and obstructive cirrhosis results. The question is still unsettled. This particular type of cirrhosis may occur without any obstruction of the ducts (Gordon, 1922 ; Poynton and Wyllie, 1926 ; Parsons and Hickmans, 1926 ; Munns, 1926), and in any case the intrahepatic biliary channels are not dilated, as might be expected in true obstructive cirrhosis. On the other hand, the disease may occur in only one of twins (Rolleston and McNee, 1929), although it might be expected that a maternal toxin would affect both. Operative treatment of the obstruction, in anatomically suitable instances, has saved a number of patients (Ladd, 1935), but it is noteworthy that some of them had symptoms (presumably caused by cirrhosis) for a considerable time after the operations. Their success means that obstruction may play an important part in the outcome of the disease, but does not prove that atresia causes the cirrhosis.

Whatever the cause, the result is a mixed unilobular and intralobular cirrhosis, with proliferation of small biliary vessels and the presence in the liver of much bile pigment. The hepatic cells may show degenerative changes, the bile passages vary from complete absence to the normal state. Holmes (1916) has given a detailed account of their anomalies.

The clinical features are well known, and the following case report demonstrates some of them :

Case 1. Female, aged three months at death. The parents were healthy ;

there was one sister aged two and a half years. Pregnancy and labour were normal. The birth weight was nine pounds four ounces.

At birth the attendant doctor noticed jaundice. This increased, though there were periods when it was less obvious than at other times. The urine

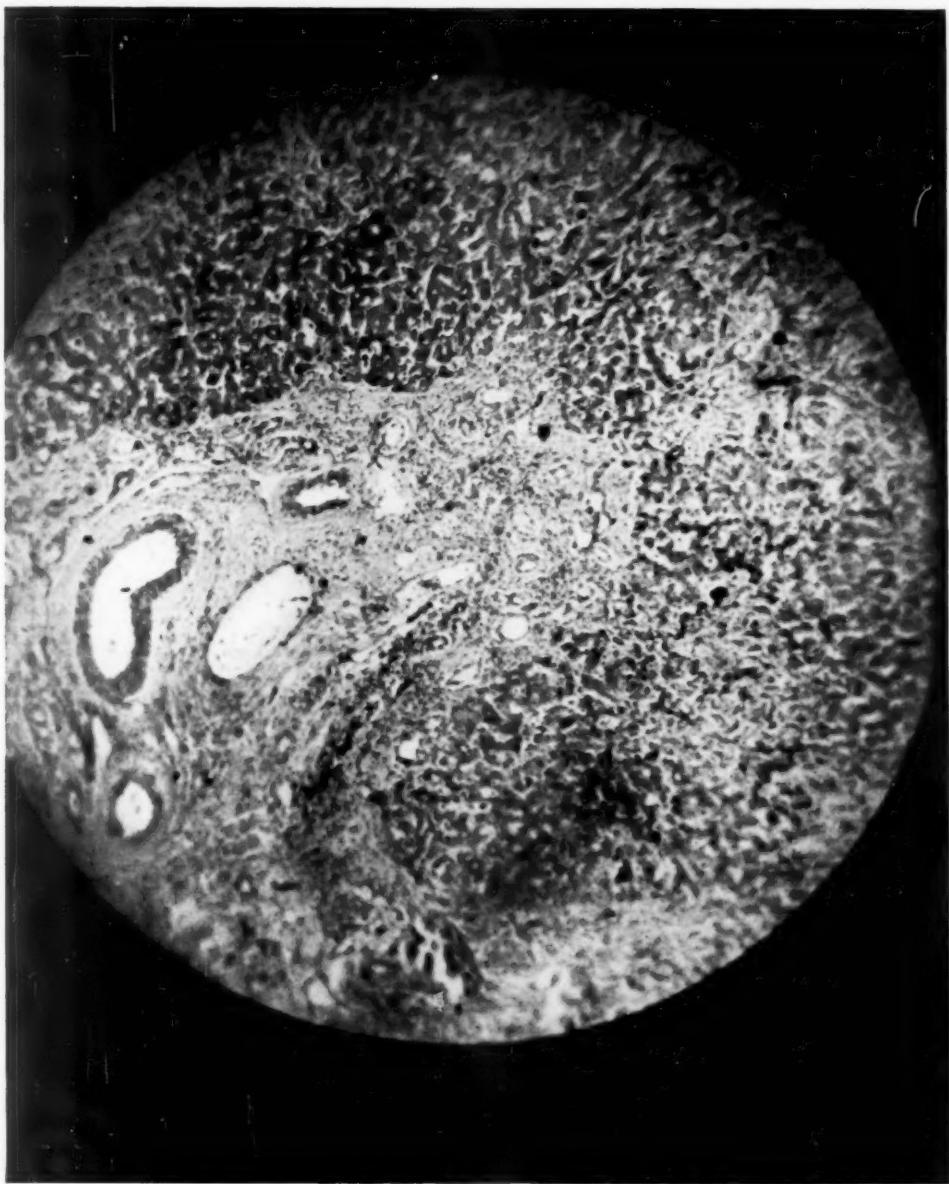


FIG. 1.—Case 1. Liver section. $\times 52$.

was dark yellow and the stools were pale and creamy. The baby was breast fed and was healthy apart from jaundice and stationary weight.

At the age of six weeks she was brought to hospital. The skin and sclerae were dark yellow ; the abdomen was distended and the liver palpable one and

a half inches below the costal margin. The faeces were almost pure white and the urine contained bile salts. She remained in statu quo for three weeks, when Mr. H. C. Edwards opened the abdomen under local anaesthesia. The liver was found to be large, dark green, firm, and sharp-edged. No gall bladder or bile duct was seen, and no duct was felt in the free edge of the gastro-hepatic omentum. The operation was well tolerated, but death occurred after slight diarrhoea and vomiting two and a half weeks later.

AUTOPSY. Wasting and uniform greenish-yellow jaundice were apparent, there was no oedema, no ascites, and no finger clubbing. The liver was smooth, firm, sharp-edged, and dark greenish-grey in colour. The gall bladder was the size of a grain of wheat, and a cord ran from it to the portal fissure. The papilla of Vater was visible, but no bile ducts could be found. On section, the liver was green, with whitish portal tracts. The hepatic veins, portal veins, and hepatic arteries were normal. No intrahepatic bile ducts were seen. Enlarged lymph glands were found in the portal fissure. The spleen was slightly enlarged and bright red ; it showed no Malpighian corpuscles. The kidneys were bile-stained, and had 'uric acid infarcts.' The meninges were bile-stained, the brain normal.

Microscopical examination of the gastro-hepatic omentum showed no bile duct. In the liver (fig. 1) large portal spaces were seen, with normal portal veins and hepatic arteries which were in a few instances accompanied by bile ducts of normal appearance. The portal spaces also contained many small veins and some arterioles ; central veins were difficult to find; sub-lobular veins appeared normal. Rather loose fibrous tissue extended throughout the portal spaces, around the lobules and to a certain extent within the lobules. Many granular pigmentary deposits of two sorts were visible : first, clusters of greenish-yellow granules lying freely in the connective tissue and in a few cases in the lumina of the bile canaliculi, which also contained mucoid material ; secondly, larger homogeneous brown nodules which were in many cases intracellular. The lobules were broken up by fibrous tissue, and contained many intercellular spaces packed with bile, but the liver cells appeared little damaged.

Non-obstructive biliary cirrhosis : Hanot's syndrome

Cirrhosis of the liver with jaundice as the predominant feature, but without obstruction of the large bile ducts, is rarely encountered. Although earlier writers (Todd, 1857 ; Hayem, 1874) had described single cases, it was not until Hanot produced his 'Étude sur une forme de cirrhose hypertrophique du foie' in Paris in 1876 that the condition received much attention.

The disease has provided so much material for controversy since then that it is profitable to examine Hanot's account. On the clinical side he described two stages. The first is the stage of onset, characterized by the simultaneous appearance of jaundice and pain or discomfort in the hypochondrium. Other symptoms are anorexia, constipation, malaise, loss of strength and fever. This stage lasts for several weeks, and is succeeded by the stage of chronic jaundice and enlargement of the liver. The jaundice is always present, but is variable, and in fact the disease is characterized by exacerbations and partial remissions of symptoms. The urine is dark, and the faeces are 'sometimes more or less decolorized, and sometimes keep their normal appearance.' The liver varies in size from time to time, it is hard and smooth, and has a sharp lower edge. In the last few months of life the organ may shrink. The spleen is often palpable ; there is no ascites except in some exacerbations and terminally. The end comes in a state of icterus grave.

That is the clinical picture, and it will be found that the two cases described below follow it fairly closely. Gilbert and Fournier (1895 *a, b*) emphasized the form of the disease in childhood, when the spleen may become enormous, the fingers may be clubbed, and growth may be arrested. They described illustrative cases in children (Gilbert and Fournier, 1895*b*) and in an adult (Gilbert and Fournier, 1897). Little has been added to the clinical description since that time. Hanot himself made little of the characteristic haemorrhagic tendency, although in the fifteen cases on which he based his essay, purpura was noted in five instances, epistaxis in four and haemoptysis in two. Three patients vomited blood, and in one of these autopsy revealed oesophageal varices. Varices cannot have caused the non-alimentary haemorrhages, and it is probable that there was prothrombopenia due either to the inability of the damaged liver to manufacture prothrombin or to acholia preventing the absorption of vitamin K (Snell, 1938).

Pathologically, Hanot described a large liver—"a block of fibrous tissue stuffed with relatively widely spaced yellowish or greenish granules." The anterior border remained sharp, no changes were apparent in the large bile passages, lymphatic glands or blood vessels, except the portal vein, which was sometimes large. The lobules varied from a quarter to four millimetres in diameter, some of them contained large quantities of bile pigment. Many "pseudo-bile canaliculi" (Hanot did not himself use this term) were present, their cells contained bile, and it was sometimes in the lumen also. Fibrous tissue was present throughout the liver in varying amounts; it was occasionally perilobular but frequently intralobular. Perihepatitis with diaphragmatic adhesions was common. He summed up the state of the liver as "an extra- and intralobular interstitial hepatitis, with catarrh and abnormal development of the biliary canaliculi."

The impression is gained of a disease with a clear-cut clinical picture and a pathological picture which was characteristic although subject to considerable variation. For example, the portal vein might be dilated and ascites might be present, whilst increasing fibrosis might reduce the huge proportions of the liver. Nodular hyperplasia was not characteristic, but perusal of the descriptions of Hanot's cases is interesting. One of the fifteen had dilated intrahepatic bile ducts and was probably obstructive in origin, insufficient details are given of another, a third was still living at the time of writing; of the twelve remaining cases, three had hobnailed livers.

Accounts of typical cases exhibiting Hanot's syndrome have been published by a number of authors. Smith (1898) described three cases with autopsies; the livers were nodular, but in two of them the fibrosis was described as definitely unilobular. In Taylor's case (1897) the liver was coarsely nodular and was microscopically a "multilobular" cirrhosis with some fibrosis extending within the masses and occasionally isolating lobules or single cells. Fiessinger, Olivier, and Albot (1929) emphasize that the cirrhosis is not strictly monolobular. Jewesbury's case (1936, 1937) exhibited "multilobular" cirrhosis with many pseudo-bile canaliculi, biliary pigmentation and infiltration with round cells.

Case 2.* Female, aged thirteen years at death. The grandparents and

* This patient was shown at a meeting of the Children's Section of the Royal Society of Medicine in 1936 (Evans, 1937*a*).

mother were healthy ; the father died of septicaemia. The patient was the fourth of seven children, the eldest died at the age of twenty years of nephritis, one brother (the fifth child) died at the age of four weeks of jaundice.

This girl's illness started at the age of eight years and ran its course in five years. In August, 1932, she had an attack of vomiting, jaundice, pale stools, dark urine and abdominal enlargement. The symptoms lasted for ten weeks. In December, 1932, she had a similar attack, and the liver was found to be enlarged two fingersbreadths below the costal margin, the spleen was just palpable, the urine contained bile salts and pigments, and the stools were pale. In January, 1933, she appeared to have recovered completely, but although she was not clinically jaundiced, the direct van den Bergh reaction was positive and the indirect 10 units. At this time she had a whitlow, the first of a long series of septic lesions from which *staphylococcus aureus* was regularly recovered on culture. The blood count at this time was normal (table 1).

TABLE I
BLOOD COUNTS IN CASE 2

YEAR	MONTH	DAY	RED BLOOD CELLS (MILLION)	HAEMOGLOBIN PER CENT.	COLOUR INDEX	WHITE BLOOD CELLS	POLYS. PER CENT.	EOS. PER CENT.	LYM. PER CENT.	REMARKS
1933	Jan.	10	4.66	92	0.98	5,400	53	2	45	—
1933	Mar.	22	2.65	50	0.94	—	—	—	—	Abscess.
1934	July	16	—	—	—	3,400	36	3	61	Abscess.
1934	July	19	—	—	—	3,400	—	—	—	Abscess opened.
1934	July	25	—	—	—	1,200	43	9	44	—
1934	July	31	—	—	—	4,300	74	6	20	Pentnucleotide 12d c.c. July 18–Aug. 1.
1934	Aug.	4	—	—	—	3,400	66	6	27	—
1934	Aug.	10	—	—	—	1,000	36	10	53	—
1934	Nov.	17	3.63	74	1.02	3,000	48	6	45	Acute nephritis.
1935	Oct.	23	5.10	100	0.98	3,000	50	5	40	Cyanosis developed.
1935	Nov.	12	4.71	96	1.02	3,400	51	5	43	—
1936	Feb.	24	5.98	102	0.85	6,200	66	4	25	—
1936	Apr.	1	5.64	102	0.90	6,400	66	8	19	—
1937	Jan.	—	—	—	—	4,600	55	1	39	Abscess.
1937	Mar.	—	5.18	106	0.98	4,000	57	2	38	One week after haematemesis.

Poly.=neutrophil polymorphonuclear leucocytes.

Eos.=eosinophil polymorphonuclear leucocytes.

Lym.=lymphocytes.

Her weight was slightly below Holt's normal, but a noteworthy feature of the illness was the way in which she recovered weight after losing it (table 2), and her nutrition was good throughout.

From May to October, 1933, she suffered from some abdominal pain and variable pyrexia, with enlargement of the liver and spleen. The liver remained large, but the spleen receded beneath the costal margin. The Wassermann reaction at this time was negative, as it was on other occasions. A slight diminution of red cell fragility was shown by the quantitative method (Dr. E. ff. Creed). Her serum did not agglutinate *B. typhosus*, paratyphosus A, B, C, melitensis or *Br. abortus*.

TABLE 2
BODY WEIGHT, CASE 2

AGE YEARS	MONTHS	PATIENT'S WEIGHT (POUNDS)	NORMAL (HOLT) (POUNDS)
8	11	47	57
9	1	52	58
9	4	48	59
9	8	61	61
10	1	57	63
10	7	57	67
11	3	72	73
11	10	68	79
12	7	68	84
12	11	69	87

In November, 1933, septic lesions appeared, and in February, 1934, she was again deeply jaundiced. An abscess over the scapula was incised, but did not heal for two months. She was severely anaemic. The jaundice eventually disappeared, but soon reappeared with further abscesses in July. She was acutely ill at this time, and developed grave leucopenia. Injections of pent-nucleotide accompanied a temporary increase of granulocytes, and she recovered.

In November, 1934, she had acute nephritis (blood urea 66 mgm. per 100 c.c., 37 mgm. six weeks later) with ascites and bilateral hydrothorax. The signs of renal failure rapidly disappeared, but she had microscopic and sometimes gross haematuria intermittently for the rest of her life—*'une véritable néphrite biliaire,'* as Gilbert and Lereboullet (1900) call it.

In August, 1935, cyanosis and dyspnoea on exertion were gradually noticed. In October she had an attack of abdominal pain, increased jaundice and fat intolerance. The liver was enlarged two, and the spleen four fingersbreadths. She had a dusky café au lait skin with considerable cyanosis of the lips, tongue, and nail-beds. The fingers and toes were clubbed. No abnormality of heart or lungs was discovered.

She recovered from the abdominal disturbance, but dyspnoea and cyanosis persisted, and the girl herself complained of breathlessness as the most severe symptom for the rest of her life. After the development of cyanosis she was never found to be anaemic. In time the leucopenia also disappeared.

In June, 1936, gross haematuria recurred, but she subsequently remained fairly well until, in January, 1937, an abscess in the leg brought her to hospital again. She returned home, but was unable to go out for walks as she was too dyspnoeic. On March 1 she vomited blood three times. She was said to have ejected between one and two pints, but when she came to hospital a week later because of increased jaundice and swelling of the abdomen and legs, she was found to be polycythaemic. The spleen and liver were still enlarged, although the latter had contracted so that it only extended one inch below the costal margin. She was ascitic, but no veins were seen on the abdominal wall. The urine did not at this time contain blood or albumin. Treatment with salyrgan caused copious diuresis and a reduction in the size of the abdomen. She was discharged, but a month later she was admitted to another hospital in cholaemia and died.

AUTOPSY.* There was jaundice and slight wasting. A small amount of

* I am indebted to the Medical Superintendent of Dulwich Hospital for allowing me to be present at the autopsy, and to take these notes.

bile-stained fluid was present in the abdomen ; all tissues were bile-stained. Abscesses were present in the following situations : one, two inches in length, in the second intercostal space, pointing subpleurally and extending to the rib ; one behind the pelvis of the right kidney ; and a large number in the kidney cortex. The larynx, trachea, bronchi and right lung were normal ; there was some interstitial haemorrhage in the left lung. The heart, aorta, inferior vena cava, common iliac veins, hepatic veins, portal vein, splenic vein and vasa brevia were normal. There was slight varicosity of the oesophageal veins, but



FIG. 2.—Case 2. Liver, cut surface, natural size.

no rupture seen. The stomach was dilated, containing half a pint of blood. The pancreas and intestines were normal. Liver: the right lobe was coarsely nodular (fig. 2) and yellow, the edges rounded, the diameter about six inches. The left lobe was small, two inches in diameter, similar in appearance, and joined to the right by a band two inches broad and four inches long and one-eighth of an inch thick, of dark red tissue (presumably capsule and attenuated liver substance). On section, nodules up to half an inch in diameter were seen, light greenish yellow in colour and separated by grey-brown matrix. Removal

of the nodules of hepatic tissue by blunt dissection showed that they were separated by thin fibrous walls which appeared to take their shape from the contiguous nodules rather than to be moulding the nodules by compression.

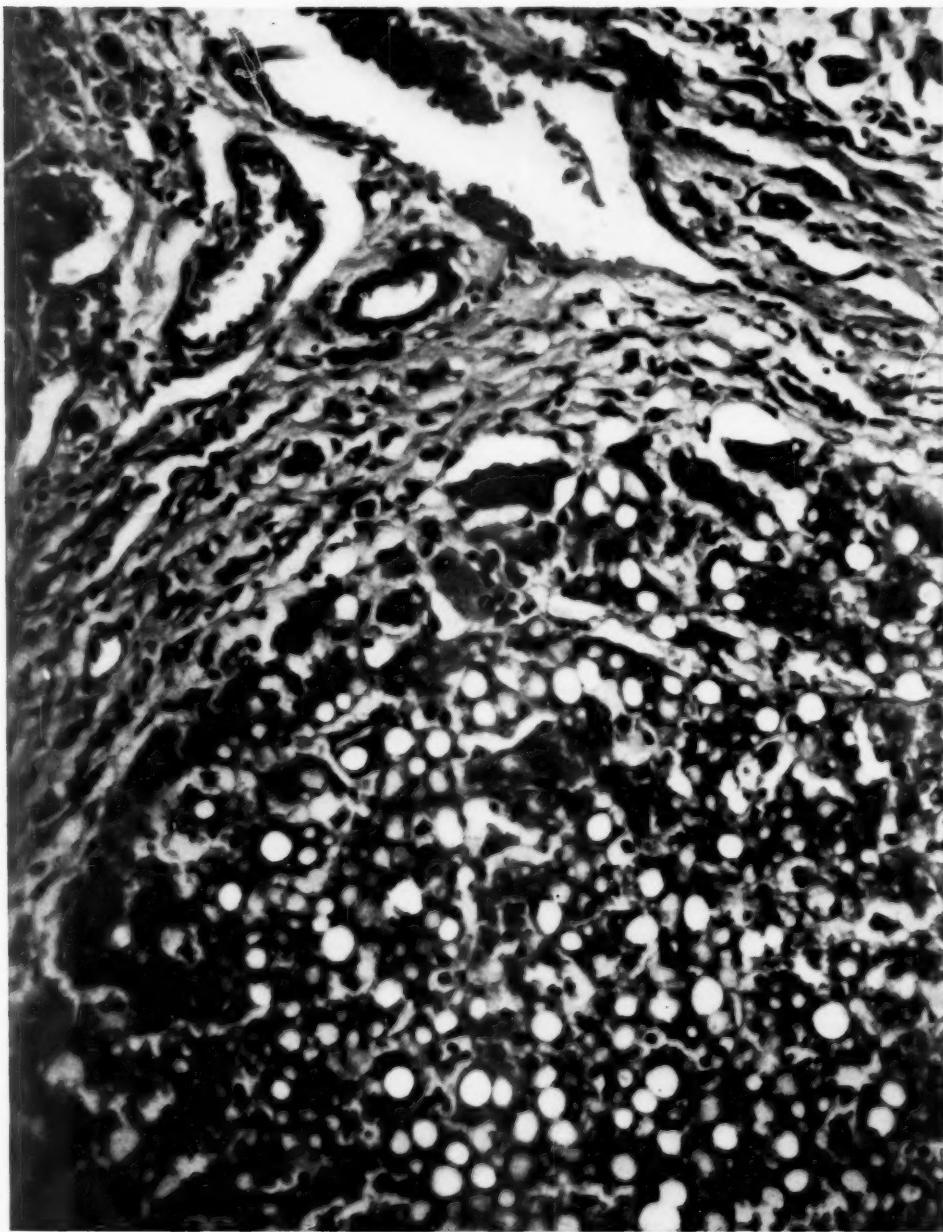


FIG. 3.—Case 2. Liver section. $\times 284$.

The spleen was ten inches long, dark red and soft.

The kidneys were large and dark in colour and pyaemic abscesses were present.

MICROSCOPICAL EXAMINATION. Liver (fig. 3) : Hepatic arterioles were normal. The portal venules varied, some being large and patent and some

compressed. The large bile ducts were normal; the smaller ducts showed desquamation of mucous membrane. Pseudo-bile canaliculi were present, but were not patent. Fibrous tissue was cellular and contained many lymphocytes and a number of thin-walled blood vessels. The liver nodules were clearly defined. The liver cells were vacuolated, otherwise in some parts normal but in others staining badly and containing deposits of greenish yellow pigment.

Left lung: the alveolar walls were thickened by congestion, leucocytic infiltration and some fibrosis.

Spleen: patchy fibrosis was present.

Kidney: pyaemic abscesses, glomerulocapsular adhesions, and patchy congestion were seen.

This patient's clinical features were those of Hanot's syndrome. The abnormalities seen post mortem were consistent with those observed in some of Hanot's cases, and with others since described. Phillips (1937) recently described a similar case which was also characterized by recurring staphylococcal infections and death from pyaemia.

TABLE 3
VAN DEN BERGH REACTIONS, CASE 2

DATE	HAEMOBILIRUBIN MGM. PER 100 C.C. (NORMAL 0·1-0·3)	CHOLEBILIRUBIN MGM. PER 100 C.C. (NORMAL 0)
1933, Jan.	+	+
1933, Oct.	0·1	—
1933, Nov.	0·6	2·8
1935, Oct.	1·1	3·1

TABLE 4
LAEVULOSE TOLERANCE TESTS, CASE 2

	BLOOD SUGAR PER CENT.	
	OCTOBER 1933	OCTOBER 1935
Before 50 gm. laevulose	0·095
Half an hour after	0·113
One hour after	0·111
One and a half hours after	0·125
Two hours after	0·114

The laboratory investigations require little comment. A positive direct and indirect van den Bergh reaction (table 3) has been noticed previously (Phillips, 1937). The laevulose tolerance test indicated some liver damage (table 4). Anaemia with leucopenia was present in this as in many other cases of severe hepatic dysfunction. The anaemia was normochromic, but it disappeared with the onset of cyanosis and was succeeded by slight polycythaemia, which has been previously noticed in Hanot's cirrhosis (Rolleston and McNee, 1929). A recurrence of nephritis did not reproduce anaemia. Leucopenia

has been observed in biliary cirrhosis, but leucocytosis is more common, as it occurred in fifteen out of twenty-five recorded cases (Rolleston and McNee, 1929 ; Hanot and Meunier, 1895 ; Taylor, 1895, 1897 ; Fiessinger, Olivier and Albot, 1929 ; Chiroy, Albot and Malinsky, 1935). Neutropenia and lymphopenia occurred in response to staphylococcal sepsis in 1934, and injections of pentose nucleotide were accompanied by a transient rise of the neutrophil count. Eventually, after the anaemia had disappeared, the white count returned to normal, the whole course of events suggesting that the marrow was potentially sound. Mild eosinophilia was sometimes present, as it was also in the second case recorded by Fiessinger, Olivier and Albot (1929).

Finger clubbing is common in biliary cirrhosis in childhood (Gilbert and Fournier, 1895 ; Taylor, 1895), although the cause has been even more obscure than in pulmonary and cardiac conditions. It has also occurred in patients with liver abscess (Locke, 1915), syphilitic stricture of the common bile duct (Rolleston, 1907), rarely in portal cirrhosis (Rolleston and McNee, 1929) and in some other diseases of the alimentary system, for example idiopathic steatorrhœa (Bennett, Hunter and Vaughan, 1932, Evans, 1934) and polyposis of the colon (Ellis, 1938).

The severe and prolonged cyanosis observed in this child suggests a connexion with pulmonary and cardiac clubbing, but the cause of the cyanosis itself is not clear. Congenital heart disease was easily ruled out. Spectroscopy revealed no abnormal pigment in the blood (Dr. R. A. McCance). Peripheral stagnation and deoxygenation of the blood cannot have been the main cause, for the femoral arterial blood was already partly deoxygenated (table 5).

TABLE 5
BLOOD OXYGEN, CASE 2, FEB. 1936 (DR. D. W. BROOKES)

Oxygen content of arterial blood	14.22 volumes per cent.
Oxygen content of venous blood	11.23 volumes per cent.
Oxygen combining power	17.94 volumes per cent.
Oxygen saturation	79.2 per cent.
Haemoglobin	14.38 mgm. per hundred c.c.

The arm-to-carotid circulation time by the potassium cyanide method was seven seconds (adult normal nine to twenty-one seconds), which also makes peripheral stagnation improbable. Another possibility is that pulmonary oxygenation was inefficient, and indeed, when the patient was placed in an oxygen tent the cyanosis was reduced when the oxygen concentration reached forty per cent., but even sixty per cent. did not abolish the purple tint. A skiagram of the chest and post-mortem examination of the lungs did not support this theory.

Keys and Snell (1938) have shown that the oxygen saturation of the arterial blood is frequently reduced in liver disease, with or without anaemia. This is considered to be due to 'an alteration in the fundamental affinity between haemoglobin and oxygen,' and the cyanosis may be temporarily reduced by the transfusion of normal blood (Judd, Snell and Hoerner, 1935).

Case 3.* A female was aged seven years at the onset of the disease. The parents were healthy ; the mother had one tubal pregnancy and one healthy daughter, and no miscarriages. The patient's health was good, except during attacks of measles, mumps and whooping cough, until in April, 1935, she developed jaundice, followed by diarrhoea and vomiting. Jaundice was continually present, with exacerbations, during the twenty-two months for which information is available, but the vomiting and epigastric pain which accompanied it became progressively rarer. The stools were pale and bulky and the urine highly coloured. At times she seemed feverish.

On examination in December, 1935, she had scleral and cutaneous jaundice. The spleen extended one and the liver three fingersbreadths below the costal margin. The urine contained albumin, bile salts and bile pigments. The blood count is shown in table 6. There was no increase in blood fragility. The serum contained 1.2 mgm. haemobilirubin and 0.08 mgm. cholebilirubin per 100 c.c. The Wassermann reaction was read as weakly positive on December 11 and positive on December 24. The mother's Wassermann reaction was weakly positive.

TABLE 6
BLOOD COUNTS, CASE 3

YEAR	MONTH	RED BLOOD CELLS IN MILLION	HAEMOGLOBIN PER CENT.	COLOUR INDEX	WHITE BLOOD CELLS	POLYS. PER CENT.	EOS. PER CENT.	LYM. PER CENT.	REMARKS
1935	Dec.	4.14	94	1.14	10,000	50	2.5	46	Reticulocytes 1.2 per cent.
1936	Mar.	4.10	82	1.0	6,600	70	1	28	Recticulocytes 1 per cent.
1937	Feb.	3.94	77	0.98	3,800	47	4	47	—

In one month the jaundice disappeared and the liver was felt to be one fingersbreadth smaller (hexamine was being given at this time). Between January and March, 1936, ten injections of 0.5 c.c. of bismostab were given. In March, 1936, she was readmitted to hospital because she complained of increased jaundice and epigastric pain. The serum contained 1.25 mgm. haemobilirubin and 3.35 mgm. cholebilirubin per 100 c.c. at this time, and the possibility of obstruction of the large bile ducts was considered. Cholecystography showed a faint shadow at twenty hours. The blood sugar was 0.066 per cent. before 50 gm. of laevulose were given, 0.088 per cent. at half an hour, 0.109 per cent. at one hour, 0.117 per cent. at one and a half hours, 0.131 per cent. at two hours. On June 3 Mr. H. C. Edwards performed a laparotomy. The gall bladder was large, white and thick-walled ; the common bile duct looked normal. Cholecystgastrostomy was performed and the operation terminated. Despite post-operative collapse of the right lung, recovery was rapid and the patient was discharged from hospital.

In February, 1937, she was seen again. She had not benefited from the operation ; jaundice was variable but always present, the urine contained bile pigments, but Hay's test was negative. The stools varied in colour. She had occasional epigastric pain and much flatulence. She was well nourished, but had not gained weight in eight months (table 7). The liver was hard but little

* This patient was shown before a meeting of the Children's Section of the Royal Society of Medicine in 1937 (Evans, 1937b).

enlarged, the spleen extended three fingersbreadths below the costal margin. The gastric residuum contained free hydrochloric acid and much bile. The Wassermann reaction was doubtful.

TABLE 7
WEIGHT, CASE 3

AGE YEARS	MONTHS	WEIGHT (POUNDS)	NORMAL WEIGHT FOR AGE (HOLT) (POUNDS)
7	10	56	52
7	11	59	52
8	1	61	53
8	2	62	53
8	4	64	54
9	0	64	58

The liver was seen at operation to be coarsely nodular. A piece was removed for microscopical examination (fig. 4). A section showed nodules of liver cells embedded in fibrous tissue, some strands of which extended into the nodules. These consisted of distorted, vacuolated cells with basophilic cytoplasm, arranged irregularly. No central veins were seen. The fibrous tissue was cellular and moderately dense; it contained a number of lymphocytes and ill-defined pseudo-bile canaliculi which appeared to be compressed. On the edges of some nodules were large cells containing groups of yellow-green granules and from one to five nuclei. The few blood vessels which could be seen were patent.

This child's illness followed a course similar to the earlier part of that in case 2, and it is reasonable to make a similar diagnosis. Syphilis must, however, also be considered. The Wassermann reaction is stated by Lange (1922) to be unreliable if there is retention of bile salts, but the mother's weakly positive reaction makes it likely that, despite the absence of stigmata, the daughter had congenital syphilis. The condition of the liver is, nevertheless, different from any recognized type of syphilitic hepatitis. It is possible, as Rolleston and Mcnee (1929) suggest, that after recovery from congenital syphilis the liver may be unusually susceptible to other agents which may cause hepatic damage.

Other types of biliary cirrhosis

The picture of non-obstructive biliary cirrhosis presented in the cases cited above resembles that of subacute yellow atrophy (e.g. Broadbent, 1905; Chisholm, 1914), and it must be admitted that the dividing line is not hard and fast, but there are some differences. Subacute yellow atrophy is caused by certain known and some unknown toxins, whilst the cause of non-obstructive biliary cirrhosis is not known. The former condition has a progressive course in fatal cases, jaundice is not always a pronounced feature, portal failure may occur early, and death is likely to supervene after weeks or months. The cirrhosis also has a progressive course, but with many exacerbations and remissions, jaundice occurs early and is frequently deep, portal failure is late in appearance, and the patient dies after years of illness. Finger clubbing is

not a feature of subacute atrophy. At autopsy the cirrhotic liver is slate green or yellow green on grey ground if nodular hyperplasia has occurred. The liver in subacute yellow atrophy consists of yellow nodules on a red back-

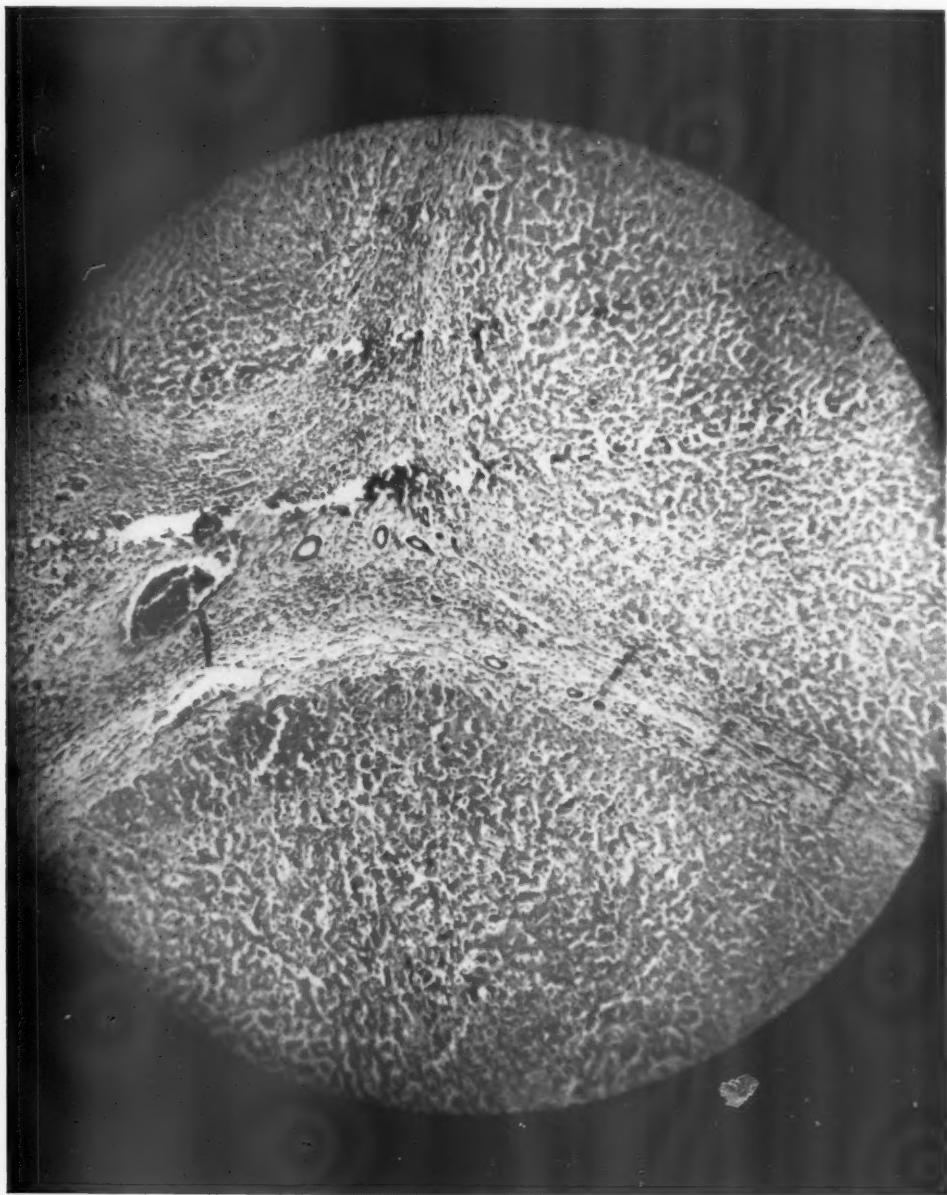


FIG. 4.—Case 3. Liver section. $\times 52$.

ground of granulation tissue. It is difficult to say how important these differences are, and it may be that biliary cirrhosis should be regarded as chronic yellow atrophy.

Mention is occasionally made of biliary cirrhosis without jaundice (e.g. Rolleston and Wyard, 1920), but few cases have been described. In the section

on hepatic cirrhosis of Nobécourt and Babonneix's *Traité de Médecine des Enfants* (1934) a picture of the microscopic appearance of perfect monolobular cirrhosis is used to illustrate the account of biliary cirrhosis. The preparation was made from the liver of a child with 'cirrhose biliaire sans ictere' described by Lereboullet in 1901. Clinically and pathologically the resemblance to the following case is striking.

Case 4.* A male, aged six years and nine months at death, was the sixth of eight children, and born of healthy parents in 1930. He suffered from occasional epistaxis, but the parents noticed nothing else wrong. At the age of four and a half years a school doctor referred him to hospital on account of enlargement of the liver and spleen.

On examination in January, 1935, he was seen to be sallow and thin, but his general condition was good and his weight thirty-three pounds. There were a few telangiectases on his face. The liver was uniformly enlarged three inches below the costal margin and was hard. The spleen extended two inches below the costal margin. Jaundice, ascites and haemorrhoids were absent. The Wassermann reaction was negative. The serum contained 0.3 mgm. haemobilirubin per 100 c.c. The blood sugar before 50 gm. of laevulose was 0.095 per cent., half an hour after it was 0.107 per cent., one hour after 0.095 per cent., one and a half hours after 0.103 per cent., two hours after 0.095 per cent.

He remained well, and gained two pounds in weight, until September, 1935, when he had two haematemeses, associated with melaena. Apart from anaemia and leucopenia (table 8) his condition appeared to be unchanged.

TABLE 8
BLOOD COUNTS, CASE 4

YEAR	MONTH	DAY	RED BLOOD CELLS MILLION	HAEMOGLOBIN PER CENT.	COLOUR INDEX	WHITE BLOOD CELLS	POLYS. PER CENT.	EOS. PER CENT.	LYM. PER CENT.	REMARKS
1935	Jan.	—	4.92	92	0.93	8,600	81	7	11	—
1935	Sept.	—	3.30	62	0.9	2,800	81	1	12	After haematemesis.
1936	Nov.	—	2.54	53	1.04	7,200	82	1	10	After haematemesis.
1936	Dec.	3	2.12	42	0.99	5,600	79	0	13	—
1936	Dec.	15	3.71	70	0.94	—	—	—	—	After transfusion.
1937	Jan.	26	2.84	57	1.01	—	—	—	—	After haematemesis.
1937	Feb.	20	3.90	80	1.03	—	—	—	—	Before haematemesis.
1937	Mar.	5	—	60	—	—	—	—	—	—
1937	Mar.	16	—	64	—	—	—	—	—	—
1937	Mar.	18	—	70	—	—	—	—	—	—
1937	Mar.	30	—	78	—	—	—	—	—	After transfusion.

After this he was again fairly well, though the liver and spleen gradually extended about an inch lower. In November, 1936, he had a large haematemesis, and was readmitted to hospital. He was pale and pyrexial (99° F. to 105° F. for two weeks), but had gained weight (to thirty-seven pounds).

* This child was exhibited before the Clinical Section of the Royal Society of Medicine two years before his death, as a case of portal cirrhosis (Newns, 1935).

Part of this gain was due to ascites, which was easily demonstrable. While he was pyrexial the cardiac apex beat was found to be external to the nipple line, gallop rhythm was present and there were loud apical and basal systolic murmurs.

The condition gradually improved, and a month later there were no definite signs of disease except enlargement of the liver and spleen. The blood count was still low, and on December 12 a transfusion of 350 c.c. of the father's blood was given. On December 16 there was another haematemesis. It was followed by a temperature of about 100° F. for two weeks, and ascites reappeared. This was present for the rest of the child's life. Progress was uneventful until January 25, 1937, when a further haematemesis occurred.

A red blood count on February 20 was nearly normal, but that evening he



FIG. 5.—Case 4. Liver. (Infra-red photograph by Miss Josephine Hunt.)

had another haematemesis. The liver and spleen appeared to become smaller a few hours (not immediately) after each haematemesis, but it was impossible to be sure that this appearance was not caused by variation in the amount of ascites.

The haemoglobin percentage was sixty on March 5, and sixty-four per cent. on March 16, so a transfusion was given on the following day, 100 c.c. of citrated blood raising the figure to seventy per cent. On March 30 it was seventy-eight per cent.

On April 1 the abdomen was opened by a left upper paramedian incision under ether anaesthesia. The spleen was removed with little difficulty, but respiration ceased rather suddenly as the wound was being closed, and despite restorative measures the boy died. He was six years and nine months old.

At autopsy nothing abnormal was found outside the abdomen, with the exception of large varicose veins at the lower end of the oesophagus. The spleen was large and firm. The liver was large and hard (fig. 5). Its

surface was smooth, but innumerable fawn-coloured nodules, mostly about one mm. in diameter, were visible beneath the peritoneum. The cut surface showed innumerable nodules of fawn-coloured hepatic tissue, some circular in section but mostly irregular, some branching, none more than two mm. in

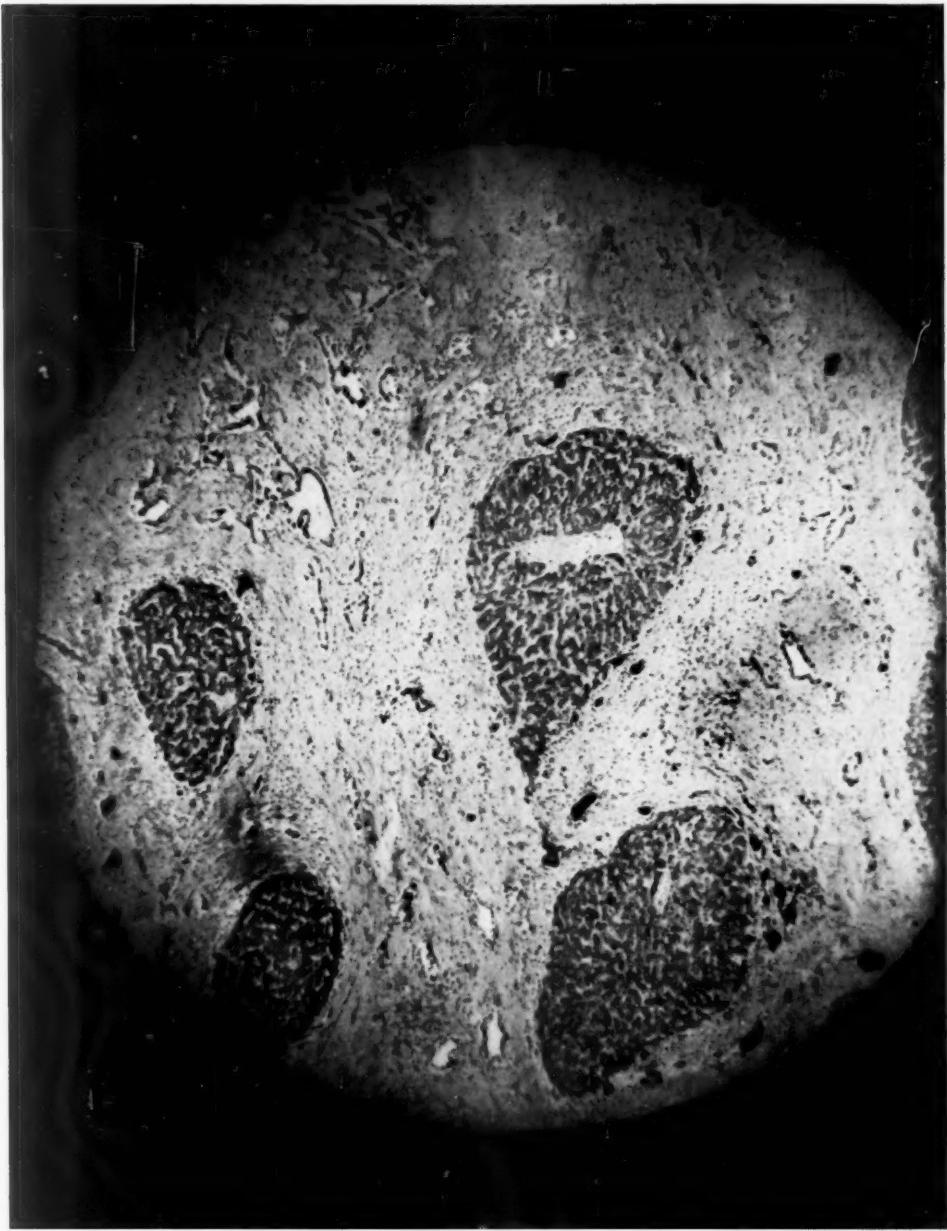


FIG. 6.—Case 4. Liver section. $\times 52$.

diameter, embedded in a hard matrix of light grey fibrous tissue. Hepatic veins were visible and were patent, though compressed. Blunt dissection demonstrated the isolated and distorted liver lobules in a thick matrix of firm fibrous tissue.

Microscopical examination of the liver showed each lobule to be separated from the next by massive interstitial fibrosis. The architecture of the lobules was not deranged, the parenchymal cells appeared normal, and central veins were visible (fig. 6). No normal portal tracts could be seen, and few vessels were visible, but isolated small arteries were present and compressed veins of various sizes were seen. There were some pseudo bile canaliculi, and also some canaliculi lined by a thin layer of flat epithelium and distended by orange-coloured bile. The fibrous tissue was dense, and there was slight lymphocytic infiltration near the borders of the lobules, but the whole was unlike the picture of degeneration, inflammation and regeneration in the first three cases.

The classification of such a case offers difficulties ; it has been pointed out that unilobular hypertrophic cirrhosis is not identical with biliary cirrhosis, and there were no obvious catarrhal changes in the canaliculi here. Clinically the course was that of portal cirrhosis, and pathologically the portal veins were seen to be compressed. It seems reasonable to describe the condition as portal cirrhosis of unilobular distribution without nodular hyperplasia. Interstitial hepatic fibrosis would be a simpler name.

Another type of liver disease that is occasionally mentioned is the 'cirrhosis' of icterus gravis neonatorum (Poynton and Wyllie, 1926). Hawksley and Lightwood (1934) found a fine perilobular fibrosis in the livers of children who survived icterus gravis for from five weeks to ten months. There were no clinical signs of cirrhosis, although signs of biliary obstruction occur transiently in some cases of icterus gravis. One case which recovered, but died at the age of ten weeks from pertussis, had no fibrosis. Pfannenstiel (1908) is cited as having described a case which proceeded to cirrhosis, but the diagnosis of icterus gravis, as the disease is defined now, is not certain. Braid (1937) described another case, in which portal cirrhosis with fatal haematemesis supervened at the age of three-and-a-half years. But here again it is permissible to doubt the original diagnosis of icterus gravis. The stools were acholic for an unusually long time (seven weeks). Anaemia, after four weeks of life without treatment, was surprisingly slight. The spleen was not enlarged until the age of five months. Erythroblastosis was not described.

One cannot doubt that a fine fibrosis may develop in the liver in icterus gravis. Such a liver may possibly be left more susceptible to toxins or nutritional disturbances at a later date. But the existence of a special type of clinical cirrhosis associated with or following icterus gravis is very doubtful.

There is also one other definite type of biliary cirrhosis. This is the infantile biliary cirrhosis, of unknown causation, which is common in certain parts of India (Mukherji, 1922). Cases are not seen in Britain, and further reference to it is not necessary here.

Conclusions

There are at least four well-attested types of biliary cirrhosis :

- A. Congenital biliary cirrhosis, with or without congenital obliteration of the bile ducts.
- B. The infantile biliary cirrhosis of Indian nurslings. This differs from

congenital biliary cirrhosis in age incidence, local occurrence, slower course and absence of obliterative cholangitis.

C. Acquired obstructive biliary cirrhosis. The signs and symptoms of this type are those of chronic, usually unremitting, obstruction of the common bile duct, enlargement of the liver and possibly of the spleen, sometimes portal failure and cholaemia. Appropriate tests show impairment of liver function.

D. Acquired non-obstructive biliary cirrhosis (hypertrophic biliary cirrhosis, Hanot's syndrome). This is a rare disease of long duration. It attacks mainly children and young adults. The onset is indistinguishable from catarrhal jaundice, but icterus does not completely disappear after the attack. Vomiting, epigastric pain and pyrexia subside, only to reappear at a later date. The course consists of a substratum of chronic jaundice and at first rather mild ill-health, with exacerbations characterized by abdominal pain, pyrexia, increased jaundice, enlargement of the liver, and vomiting. They recur at intervals of weeks or months, and usually subside in two or three weeks, but leaving the patient in a poorer state than before. The spleen becomes palpable, and in children may be enormous. The liver is at first likely to increase in size with each exacerbation. The stools vary, being usually pale and at times acholic. The urine contains bile salts and pigments. The van den Bergh reaction is biphasic. The blood picture is variable. Anaemia may be macrocytic or microcytic, but is frequently normocytic. There may be no anaemia, and polycythaemia is not unknown. Leucocytosis is common, but leucopenia occurs in a minority of cases. Liver function tests show impairment.

As the patient's condition deteriorates, complications occur—perhaps nephritis or staphylococcal infections, or in children clubbing of the fingers. In children growth is eventually stunted, but in general, anorexia and wasting are surprisingly slight. Every patient is likely to have haemorrhage from some site. The liver becomes gradually smaller. In time, usually years after the onset, massive haematemesis and ascites may develop, and the picture of fluctuating portal failure supervenes on fluctuating biliary failure. At this stage the end is not far off, but the individual may struggle on for a few months or a year, and then die in cholaemia or as result of haematemesis or from intercurrent infection. Pathologically the liver shows a diffuse degenerative hepatitis with fibrosis distributed around and within the lobules; the picture may be much altered by nodular hyperplasia. The tissues are bile-stained, there are many pseudo-bile canaliculi, and the true intrahepatic bile ducts show catarrhal changes and bile plugs. The extrahepatic biliary channels may have some signs of past inflammation, but are free from obstruction.

Thanks are due to Dr. Wilfrid Sheldon for allowing the publication of accounts of these cases.

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THE ASSOCIATION OF GALL-STONES WITH ACHOLURIC JAUNDICE IN CHILDREN

REPORT OF A CASE IN A CHILD AGED THREE YEARS
WITH A NOTE ON THE CRISES OF ACHOLURIC JAUNDICE

BY

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The majority of cases of acholuric jaundice in adults are associated with gall-stones. In children the same association is mentioned in some of the text-books, although the literature contains references to few cases, the following ten cases being all that a search has yielded.

Two cases, both aged about fifteen years, are reported from the Mayo Clinic (Potter, 1928); splenectomy was performed for 'haemolytic anaemia' and gall-stones were found at operation, but no other details are available. Murray-Lyon (1935) reports a case of acholuric jaundice in a boy aged ten years; multiple-facetted gall-stones were found unexpectedly when splenectomy was performed. Snelling and Brown (1936) report a similar case in a child of six years. In the case reported by Brooks, Clinton and Ashley (1935) of a child aged four years, gall-stones in a chronically inflamed gall-bladder were found at operation; their presence had not been suspected, although some of the symptoms described, such as intense icterus, may well have been due to them. Roberts (1938) mentions two sisters, aged twelve and fourteen years; in both gall-stones were diagnosed radiologically and subsequently removed. The only available series of children who have been splenectomized for acholuric jaundice is that of Barrington-Ward (1937). In his series of ten cases under twelve years, three (30 per cent.) were found to have gall-stones, the youngest of these being six years. In none had their presence been suspected prior to operation (personal communication).

The small number of the reported cases in the literature is thus in contrast to Barrington-Ward's findings. This may be due to failure to examine for the presence of gall-stones when splenectomy is performed. If, as Barrington-Ward's figures suggest, acholuric jaundice in children is often associated with gall-stones, occasional cases would be expected in children, as in adults, to present with symptoms due to the gall-stones. Up to the present, however, this possibility does not appear to have been recognized. It is the purpose of this communication to draw attention to it.

The diagnosis of gall-stones in children

Gall-stones, from whatever cause, are uncommon in children. Potter in 1928 was able to collect only 141 cases from the literature. An analysis of

his series shows that the majority fall into one of two categories : (1) Foetuses and young infants, when the gall-stones of pigment type are found at autopsy in subjects dying from some unrelated complaint. Here the gall-stones rarely give rise to symptoms. (2) Children usually in the second decade of life, when the adult type of disease with cholecystitis and lithiasis occasionally occurs and enables a pre-operative diagnosis sometimes to be made.

Acholuric jaundice is not an uncommon disease : there have been nineteen cases at the Hospital for Sick Children, Great Ormond Street, during the past ten years. If the conclusion is accepted that in these cases gall-stones are common, there must exist a third category—children of any age with acholuric jaundice associated with gall-stones of the pigment type. These stones being radio-opaque should be easily demonstrated ; Roberts' two cases appear to be the only previous ones in which use was made of this fact in children.

Previously the diagnosis of cholelithiasis in a young child during life has only been made either when a stone was passed per rectum or at operation. I have been able to collect seven such cases from the literature in children under four years.

DATE	AUTHOR	SEX	AGE	REMARKS
1879	ANDUARD	?	Under 4 years	Colic : stone in faeces.
1880	MASSIE	F	4 years	Gall-bladder symptoms : stone in faeces.
1882	WALKER	M	3 months	Stone in faeces.
1884	RICARD	?	Under 4 years	Colic : stone in faeces.
1925	SNYDER	M	4 years	Cholecystitis and lithiasis found at operation for acute appendicitis.
1927	POTTER	?	3 years	Cholecystectomy (no details available).
1935	BROOKS et al.	M	4 years	Acholuric jaundice : gall-stone unsuspected until operation.

Case report

A female child aged three years and a quarter was admitted to the Hospital for Sick Children on March 4, 1938, on account of increasing jaundice. Six days previously the jaundice had first been noticed, and on that day there had been some mild abdominal pain, but no nausea or vomiting, and the child had seemed well and had taken her food normally. A day or two later it was noticed that the motions were pale and the urine dark. There had been no further pain, and apart from the increasing jaundice the child had not seemed unwell.

Past history.—The patient had had pertussis a year previously and tonsillectomy six months previously. There had been no previous jaundice or anaemia, the child having always been healthy.

Family history.—The parents were unrelated. The mother suffered from chronic nephritis, from which she has since died ; at autopsy there were no findings suggestive of haemolytic disease. Neither parent had ever suffered from jaundice or anaemia, nor was there any history of these complaints amongst their relations. This inquiry included twenty-three first cousins of the patient. There had been one sibling, born a year before the patient. It was a month premature following an ante-partum haemorrhage, and lived one week.

Condition on admission.—A well-developed child, weighing twenty-eight pounds (normal for age thirty-four pounds). She was in apparently normal health except for intense icterus. The tongue was furred. The liver was palpable two fingersbreadths below the costal margin, was of normal consistency and was not tender. The spleen was not palpable. The temperature and pulse rate were normal.

URINE : bile salts and pigments ++, no excess urobilin.

VAN DEN BERGH (direct) : ++.

SERUM BILIRUBIN : 39 units ; one week later, 9.5 units (normal up to 0.4 units).

PLASMA PHOSPHATASE : 23.5 units ; one week later 22.5 units (normal 5-20 units).

LAEVULOSE LIVER FUNCTION TEST (oral) : normal.

SEDIMENTATION RATE : 33 mm. in one hour.

A tentative diagnosis of catarrhal jaundice was made, although it was recognized that there were two facts which were not typical : the onset with little or no constitutional upset and the unusually intense degree of icterus. However, the gradual return to normal of the colour of the urine and faeces appeared to confirm the diagnosis.

On March 18, 1938, the child was discharged home. She was then well, having gained one pound in a fortnight ; icterus was just discernible ; there was no anaemia clinically (no blood count was done at this time), but the liver was still enlarged.

On March 24, 1938, she was re-admitted with the following history : Three days after discharge she became unwell, drowsy, complaining of toothache and pains in the limbs ; she appeared pale. Next day the urine was ' tea-coloured ' and pallor was now severe. On the day before re-admission she became ill with fever and sweats ; she passed several liquid stools which were almost black in colour.

Condition on admission.—The child was almost moribund, with gross pallor and a slightly icteric tinge. The liver was more enlarged than previously, but was not tender. The gall-bladder was not felt. The spleen was easily palpable. The temperature was normal and the pulse rate 140. The urine showed a slight excess of urobilin ; bile salts and pigments were absent ; there were 10 mgm. per cent. of albumin present. The faeces contained no blood ; bile pigments were present.

BLOOD PICTURE : Haemoglobin 20 per cent. ; red blood cells 1.06 millions ; normoblasts 0.5 per cent. ; reticulocytes 0.1 per cent. ; microcytosis ++, anisocytosis ++, poikilocytosis +. White blood cells 19,300 per c.mm. (polymorphs 55 per cent. ; lymphocytes 29.5 per cent. ; monocytes 8 per cent. ; basophils 1 per cent. ; neutrophil myelocytes 5 per cent. ; metamyelocytes 1.5 per cent.). Platelets 197,240 per c.mm.

On clinical examination and before a haematological examination was available, a diagnosis was made of yellow atrophy of the liver complicating a previous catarrhal jaundice. Treatment was thereupon instituted as follows : by means of an intravenous drip alternate transfusions were given of 10 per cent. glucose in saline, and of whole blood (mother as donor, the mother and child both being group A). In this way she received 100 grammes of glucose and 600 c.cm. of blood during the course of the twenty-four hours. Following this her condition improved swiftly and her haemoglobin rose to 60 per cent. (table 1).

TABLE I
BLOOD PICTURE IN A CASE OF ACHOLURIC JAUNDICE SHOWING EFFECT OF BLOOD TRANSFUSION DURING A HAEMOLYTIC CRISIS, AND OF SUBSEQUENT SPLENECTOMY. NOTE DISAPPEARANCE OF SPHEROCYTOSIS SOON AFTER RECOVERY FROM THE CRISIS

Days after crisis	0	1	2	4	9	16	20	29	35	42	43	48	58	136	330
Haemoglobin per cent. (Haldane)	20	1.06	45	55	60	58	53	62	62	62	64	72	72	75	75	75	85	
Red blood cells, millions	2.86	3.5	3.16	2.9	3.04	3.34	3.48	4.64	4.42	4.25	4.42	4.64	4.42	4.25	
Colour index	1.0	0.9	0.9	0.9	1.0	0.9	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	
Reticulocytes per 100 R.B.C.	7.6	1.0	10.8	10.1	9.6	18.0	18.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	
Normoblasts per c.mm.	300*	351	0	0	0	65	0	0	0	0	0	0	0	0	
Erythroblasts per c.mm.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Megaloblasts per c.mm.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Fragility limits (normal 0.30-0.39 per cent.)	0.36-	0.60	0.60	0.60	0.39-	0.60	0.54	0.33-	0.33-	0.33-	0.33-	0.33-	0.33-	0.60	
<hr/>																				
Anisocytosis	++	++	++	++	++	++	++	++	++	++	++	++	++	++	
Spherocytes	
Van den Bergh (direct reaction)	
Serum bilirubin (normal, up to 0.4 units)	
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White blood cells, thousands	19.3	5.2	9.5	8.8	6.5	6.4	6.4	11.6	10.8	13.6	13.6	13.6	13.6	8.2	
Polymorphs, per cent.	55	54	50	58	56	56	56	76	54	70	43.5	43.5	43.5	43.5	
Basophils	1	0.5	2	0	0	0	0	0	0	2	0	0	0	0.5	
Eosinophils	0	0.5	6	2	0	4	4	2	2	6	2	2	2	1.5	
Lymphocytes	29.5	27	32	32	38	38	38	16	16	16	16	16	16	16	
Monocytes	8	8.5	6	10	2	2	2	6	6	11	11	11	11	36.5	
Myelocytes	5	0.5	0	0	0	0	0	0	0	0	0	0	0	4.5	
Metamyelocytes	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	
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Platelets, thousands	197	
																			506	
																			545	
																			244	

* These figures are approximate.

Meanwhile Dr. D. G. ff. Edward reported that the majority of the red cells were densely staining microcytes (microspherocytes). Microspherocytosis was obvious in the wet films for the first nine days after the crisis ; thereafter the red cells appeared normal apart from well-marked anisocytosis and polychromasia. On the twenty-second day after the crisis a Price-Jones curve was constructed (fig. 1), and the following dimensions of the red cells estimated :

Mean corpuscular haemoglobin : 25.5γγ (normal 27-32).

Mean corpuscular diameter : 7.3μ (normal 6.7-7.7).

Coefficient of variation : 10.2 (normal 5.7-7.3).

Mean corpuscular volume : 110 μ³ (normal 80-94).

Mean corpuscular thickness : 2.6μ (normal 1.7-2.5).

Diameter-thickness index : 2.8 (normal 2.4-4.2).

Volume-thickness index : 1.45 (normal <1.5 (Hill, 1938)).

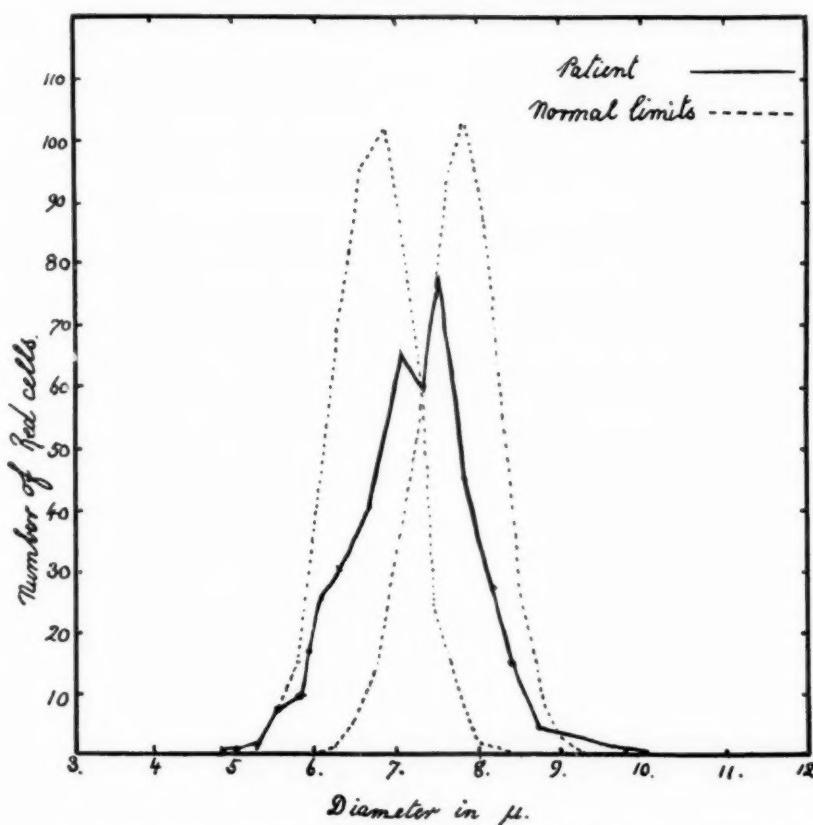


FIG. 1.—Price-Jones curve, twenty-second day after haemolytic crisis. Normocytosis and anisocytosis shown. At this stage the reticulocytes numbered 10 per cent., accounting for the number of macrocytes present, 5 per cent. of the cells having diameters of over 9μ. (By courtesy of Dr. C. J. C. Britton.)

These measurements confirm, on the whole, the absence at this time of spherocytosis : the cells are of normal average diameter, the diameter-thickness index is well within normal limits, and Haden's volume-thickness index is just below the upper limit of normal as estimated recently by Hill (1938). In contrast to this change in shape undergone by the red cells following recovery from the crisis, their fragility was constantly increased [table 1, normal fragility limits for this age (washed cells), 0.30 to 0.39 per cent.].

The persistent fragility and high level of the reticulocytes (table 1) now suggested that the crisis had been superimposed upon a chronic haemolytic process. With this in mind the original attack of obstructive jaundice was reviewed, and the possibility arose that it had been due to a gall-stone. Cholecystography failed to demonstrate the gall-bladder, but a shadow suggestive of a stone was seen in the region of the gall-bladder.

Operation.—After a blood transfusion from a donor unrelated to the patient, splenectomy was performed by Sir Lancelot Barrington-Ward. A stone was found at the junction of the cystic and common ducts, and this, along with the gall-bladder, was removed. Convalescence was uneventful.

Pathological report.—(Dr. D. N. Nabarro.)—

SPLEEN : weight ninety-seven grammes. Histology : the splenic pulp is largely replaced by a suffusion of blood. The Malpighian bodies are prominent, many with large germinal centres. The appearances are those seen in acholuric jaundice.

GALL-BLADDER : small and contracted with considerable thickening of the walls. Histology : the muscular layer is increased, the serosa oedematous and congested, and the epithelium normal. There is little evidence of inflammation. The appearances suggest simple hypertrophy due to obstruction, with slight inflammatory reaction in the mucosa.

GALL-STONE : 1×0.5 cm., the appearance being that of a pigment stone.

Result.—The usual satisfactory effect of splenectomy on the blood picture was seen (table 1), and the signs of abnormal haemolysis disappeared. One year later the child was very well. The liver was now not enlarged. The only abnormal findings were persistent anisocytosis and fragility of the red cells.

Discussion

Three features of the case require comment : the familial aspect of the disease, the nature of the crisis and the transient appearance of microspherocytosis.

1. No evidence was obtained that other members of the patient's family suffered from acholuric jaundice. Although both the child's father and mother were somewhat anaemic (haemoglobin 75 per cent. and 70 per cent. respectively), the fragility of their red cells was found to be normal, using a qualitative method. No attempt was made to employ a more delicate method in order to uncover slight departures from the normal, as suggested by Vaughan (1936), nor was it possible to estimate the fragility of the red cells of other relatives of the patient.

2. The history of dark motions and dark urine forms the chief evidence upon which is based the assumption that the acute anaemia was caused by a haemolytic process. Actually the signs of active haemolysis were largely absent by the time the child was seen in hospital, as the level of urobilin in the urine was then only moderately raised. The absence of blood in the faeces appeared to rule out the possibility that a cryptic haemorrhage had caused the sudden development of anaemia. The absence of any past history of anaemia or of jaundice (apart from the obstructive jaundice accounted for by the gall-stone), is noteworthy in contrast to the presence of the pigment stone, which is strongly indicative of a long-standing haemolytic process.

3. Microspherocytosis was apparent in the blood films during the first nine days following the haemolytic crisis. Thereafter the red cells were shown to be within the limits of normality in this respect, though their dimensions showed perhaps a slight tendency to what Vaughan (1937) has described as megalospherocytosis ; that is, a thick cell with a normal or large diameter and so having a large corpuscular volume. This change in shape of the red cells after the crisis was not reflected in their fragility, which remained constantly raised.

It is not proposed to discuss here the whole question of the significance of spherocytosis and of its relation to fragility. Much recent work on this subject has shown that it is more complex than had been thought hitherto. It will suffice to indicate the contributions which the study of this case can make towards the different theories.

Briefly there are two views : one regards spherocytosis as the essential abnormality which absolutely distinguishes familial acholuric jaundice from the other haemolytic anaemias. This theory was initiated by Naegeli in 1919 and elaborated by Haden (1934).

The opposite view is that spherocytosis is not pathognomonic of any one form of haemolytic anaemia, but may occur whenever active haemolysis is present. On this theory spherocytosis results from the effect of haemolysins on the red cell. Convincing clinical and experimental evidence in favour of this view has recently been produced by Dameshek and Schwartz (1938).

Whichever view of the significance of spherocytosis is accepted, it has usually been concluded that fragility was a manifestation of, and hence ran parallel to, spherocytosis. Haden and Dameshek and Schwartz all emphasize this. A number of workers, however, have shown that in acholuric jaundice splenectomy usually abolishes the spherocytosis while leaving the fragility unaltered (Hawksley, 1936 ; Vaughan, 1937). This fact favours an alternative view, that fragility, not spherocytosis, is the pathognomonic feature of acholuric jaundice. It is important to emphasize that in acholuric jaundice the fragility tends to be persistently raised, because in acute haemolytic processes, such as that of Lederer, increased fragility may occur temporarily (Parsons and Hawksley, 1933 ; Joules and Masterman, 1935), but does not persist after the haemolysis is over (Dameshek and Schwartz, 1938).

On the basis of these various opposing theories, the facts of the reported case may be regarded as follows :

The appearance of spherocytosis at the haemolytic crisis, and its virtual disappearance subsequently, is in keeping with the view that spherocytosis is associated with active haemolysis, rather than that it is the cause of it. At the same time it is worthy of note that no support is furnished in favour of the existence of haemolysins in this disease. Thus two blood transfusions, one just after the crisis and one later, proceeded without reaction, the first being even particularly effective therapeutically. Before each transfusion the patient's serum was mixed with the donor's red cells for fully half an hour without haemolysis being observed. These findings are in contrast to those of Dameshek and Schwartz and others, who have demonstrated haemolysins in the patient's serum and have proved that blood transfusion in these cases is ineffective or even dangerous.

That the fragility of the red cells remained persistently raised after their

shape had returned from spherocytic to normal argues against the theory that fragility is a function of spherocytosis. It favours, on the contrary, the view that such a persistent fragility is the essential feature of one group of the haemolytic anaemias.

There remains to discuss the justification for describing the case as one of acholuric jaundice. According to Vaughan (1936), acholuric jaundice can be clearly differentiated from all other haemolytic anaemias, as every case can be shown to have abnormal fragility, as also have some of the relatives. As has been stated, the exclusion of this familial aspect of the disease was not complete, and its apparent absence hence of no significance. On the other hand, the abnormal fragility of the patient's cells was persistent and well marked. The chronic nature of the haemolytic process was shown by the reticulocytosis which persisted during the six weeks between the crisis and splenectomy, and also by the presence of a pigment gall-stone. Lastly the splenic histology was characteristic of acholuric jaundice. In spite, therefore, of the striking transience of the spherocytosis, this case falls within the acholuric jaundice group.

A NOTE ON THE CRISES OF ACHOLURIC JAUNDICE

Many authors emphasize that severe degrees of anaemia are rarely met with in acholuric jaundice. Some cases, however, are on record in which the haemoglobin has been reduced to 20 per cent. or less during an acute haemolytic crisis (Kahn, 1913 ; Nobel, 1914 ; Götzky and Isaac, 1914 ; Salmons, 1926 ; Jörgensen and Warburg, 1927 ; Scott, 1935 ; Murray-Lyon, 1935 ; Dedichen, 1937). A study of these cases of severe crises results in the following conclusions :

1. Severe crises occur chiefly in children.
2. There is usually fever and the appearances of an infection, though no infective agent is discoverable.
3. Intestinal symptoms are common, such as vomiting, diarrhoea, and abdominal pain.
4. Jaundice is slight.
5. Blood picture : the blood picture at the height of the crisis in ten representative cases is set out in table 2. In all these cases the haemoglobin was reduced to below 30 per cent. Although the blood picture in these ten cases is not uniform, yet the following description can usefully be given.

RED CELLS : Normoblasts and megaloblasts are often numerous. The reticulocyte count at the height of the crisis is generally normal. Microspherocytosis is usually marked.

WHITE CELLS : Some degree of leucocytosis is common, often absent and occasionally extreme (cases 2, 3, 9). The most striking feature of the differential count is the presence of primitive granulocytes, myelocytes, and less often metamyelocytes and myeloblasts in the majority of cases.

6. Effect of blood transfusion : eight out of the ten cases received blood transfusions, and in seven of these an immediate clinical improvement followed,

TABLE 2
BLOOD PICTURE IN TEN CASES OF ACHOLURIC JAUNDICE WITH SEVERE HAEMOLYTIC CRISIS. NOTE THE
TENDENCY TO LOW RETICULOCYTE LEVEL BEFORE TRANSFUSION

CASE	AUTHOR	AGE	HAEMO-GLOBIN, PER CENT.	RED BLOOD CELLS, MILLIONS	COLOUR INDEX	SPHEROCYTOSIS OR MICROCYTOSIS	RETICULOCYTES		NORMO-MEGALO-BLASTS, PER CENT.	MEGALO-BLASTS, PER CENT.	WHITE BLOOD CELLS, THOUSANDS	PRIMITIVE WHITE BLOOD CELLS
							BEFORE TRANS-FUSION, PER CENT.	AFTER TRANS-FUSION, PER CENT.				
1	Götzky and Isaac	9	20	1.1	0.9				12.5	11.5	27.3	Myelocytes, 9 per cent.
2	"	3	12	1.2	0.5	+		4.6	3.5	74.7	Myelocytes, 15.5 per cent.	
3	Jørgensen and Warburg	9	20	1.1	0.9	++			0	0	340	Myelocytes ++
4	Scott	2	20	1.0	0.9	++	0	20-25	0	0	7.6	Myeloblasts +
5	"	9	16	0.8	1.0	++	0	4-10	++	11	Myelocytes, 12 per cent.	
6	"	5	18	0.8	1.1	++	2	10-15	++	5	Myelocytes, 5 per cent.	
7	"	7	26	1.5	0.9	++	2	40	++	0	0	Myeloblasts 0
8	Murray-Lyon	10	16	1.7	0.8	++	<1	4-21	0	0	4.4	Metamyelocytes 0
9	"	3	27	1.7	0.8	++	<5	41	++	6	0	Myelocytes ++
10	Gardner	3	20	1.1	1.0	+	0.1	1-18	0.5	0	50	Metamyelocytes, 5 per cent.
											19.3	Metamyelocytes, 1.5 per cent.

which coincided with a sudden and sustained rise in the reticulocyte count from a low figure to from 4 to 41 per cent. (The exception was case 8, which only responded in this way after a second transfusion. Case 9 was the only one with a fairly high reticulocyte count at the crisis, but here transfusion raised the reticulocyte level from 5 to 41 per cent).

From the records of these cases it is difficult to avoid the conclusion that the recovery which followed transfusion was not merely coincidental. Nevertheless, that recovery can occur spontaneously from even the severest crises, is shown by cases 1 and 2, in which recovery occurred, though more slowly than in the remaining eight cases which received transfusion.

Differential diagnosis of acute haemolytic anaemia

A description of the acute haemolytic anaemia of Lederer as seen in childhood has recently been given by Parsons (1938). His description resembles in a striking way that given above of the crises of acholuric jaundice. Both diseases occur often in the young, and the symptomatology of their onset is similar. As regards the blood picture, Parsons describes what he terms the 'aregenerative phase,' in which reticulocytosis may at first be absent, red cell regeneration being preceded by a leucocytosis with many primitive granulocytes. Finally, cases of Lederer's anaemia respond immediately to blood transfusion, in the same way as do the majority of severe acholuric crises.

This similarity between the two types of acute haemolytic anaemia has been noted by others. One of Murray-Lyon's cases was at first thought to be a Lederer's anaemia. Vaughan (1936) stresses the inadequate fragility investigations recorded in published cases of Lederer's anaemia, and considers that these were probably examples of acholuric jaundice. West-Watson and Young (1938) also emphasize the slender evidence on which differentiation of the two diseases is supposed to be made.

It has been shown that an acholuric crisis or a Lederer's anaemia may give no past history of illness, may present an identical clinical and haematological picture, may have fragile red cells and may respond to transfusion. Micro-spherocytosis is usually, possibly always, present during a crisis of acholuric jaundice, and since macrocytosis is said to be characteristic of Lederer's anaemia this is probably an important differential point. The work of Dameshek and Schwartz, however, suggests that spherocytosis may occur in any acute haemolytic process, so that its presence cannot be diagnostic of any particular type. It would seem, therefore, that the two types of acute haemolytic anaemia may be indistinguishable during the crisis.

After recovery from the crisis a Lederer's anaemia returns haematologically to normal, so that the two following criteria should be satisfied :

- (1) Differential fragility curves should be normal. (No cases of acholuric jaundice with normal fragility by the differential method has been described.)
- (2) Reticulocytosis and other evidence of abnormal haemolysis should be persistently absent.

Published cases of Lederer's anaemia have sometimes been fairly adequately

investigated as regards the second of these criteria (Parsons and Hawksley, 1933 ; Joules and Masterman, 1935), but not the first. This requires to be done.

Meanwhile it would seem best to regard acute haemolytic anaemia of the type under discussion as a syndrome. This syndrome occurs in several conditions in which the erythron is persistently abnormal, e.g. spherocytic, fragile or sickled. Occasional cases of leukaemia present the same syndrome, and in them blood transfusion may also bring about a remission.

The evidence that the syndrome also occurs in the absence of these conditions (i.e. Lederer's anaemia) is at present suggestive but inconclusive.

Summary

1. Gall-stones are probably more commonly associated with acholuric jaundice in children than is generally recognized.
2. Such cases may present with symptoms due to the gall-stones.
3. Diagnosis of such cases is simple, as the pigment stones are radio-opaque.
4. A case is described illustrating these points.
5. Microspherocytosis disappeared soon after a crisis : fragility was persistently raised. The significance of these facts is discussed.
6. Blood transfusion in acholuric jaundice is discussed.
7. Severe crises of acholuric jaundice tend to resemble those of Lederer's anaemia. The differential diagnosis is discussed.

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THE AFTER-HISTORY OF PREMATURE INFANTS

WITH SPECIAL REFERENCE TO THE EFFECT OF THE BIRTH WEIGHT ON THE WEIGHT CHART

BY

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The literature contains numerous studies of the weight of children from infancy onwards, and of the factors, social and environmental, which may affect that weight. One highly important factor, however, which seems to affect the weight throughout childhood, appears to have been omitted from these studies, and that is the weight at birth.

Hess (1934) in an extensive and careful study of the development of prematurely-born children (which he defines as weighing five and a half pounds or less at birth, irrespective of the duration of gestation) compares the weight of prematurely-born children at various age periods with that of their full-term siblings, and comes to the conclusion that the former consistently weigh less than the latter until the age of four, after which they conform fairly closely to the weight curves of the full-term brothers. He also showed that those babies in the series which are very small at birth gain weight relatively less rapidly than larger babies in the series of the same sex. He also states that the curve for increase in height in the premature series lags behind the curve of the full-term siblings in the same way as the weight curve. How far the present figures agree with these results will be seen in the tables to follow.

Present study

Records have been kept of a hundred and fifty-two consecutive children above the age of one year who at birth weighed five and a half pounds or less, irrespective of the duration of gestation, and the record compared with that of a control series of a hundred and fifty-two consecutive children above the age of one year who at birth weighed eight and a half pounds or more. The children had a wide variety of ailments and irrespective of ailment, with four exceptions to be mentioned, all were included in the two series : all were attending the Out-Patient Department of the Hospital for Sick Children at Great Ormond Street for medical conditions.

For convenience the series of children which at birth weighed five and a half pounds or less will henceforward be termed the 'premature series,' and the series of those which weighed eight and a half pounds or over at birth will be termed the 'control series.'

Four cases were excluded from the series on account of the fact that they were suffering from conditions which might be expected to have a gross effect on the weight chart : two of those were in the premature series, two in the control series. The following are the details of the cases :

PREMATURE SERIES

1. 1 case of congenital pulmonary stenosis ; aged six years five months ; birth weight three pounds ; sixteen pounds underweight ; mental defect.
2. 1 case of gross obesity in a girl aged eleven years six months. Birth weight two-and-a-half pounds ; thirty-eight pounds overweight ; precocious menstruation.

CONTROL SERIES

1. 1 case of congenital morbus cordis in a girl aged five years eight months. Birth weight ten pounds ; nine pounds underweight.
2. Case of congenital morbus cordis in boy aged six years one month. Birth weight eight-and-a-half pounds ; 1½ pounds overweight.

It is emphasized that apart from these four cases the cases were taken consecutively regardless of diagnosis.

The weights were taken with the children naked, or with a vest only : one reading only was used for the study, and that was the reading taken at the first attendance in the case of new patients, or in the case of patients who had attended previously before seeing the writer, the reading taken on the first attendance at which he saw the patient.

A source of error lies in the fact that it was necessary and inevitable that the mother's word should be taken with regard to the birth weight, period of gestation, presence of toxæmia during the pregnancy, and the incidence of infectious fevers. Any case in which the parents were doubtful about the birth weight was discarded from the series. It is unlikely that in a series of 150 cases with controls the error arising in this way would be an appreciable one.

Presentation of results

The study is in no way an attempt to give the average weight of children of varying birth weights : it is a comparison only, and by comparison it is intended to show that the weight at birth has a considerable effect on the weight in later childhood. All figures of weights therefore are given in terms of the number of pounds more or less than the normal for the age and sex, using Holt's figures for the normal. The figures are based on those figures of Holt's which are appropriate to the sex of the children studied, and hence it is possible

on the graph (fig. 1) to give one line of normality for a study which includes children of both sexes. In other words, supposing that there are ten children of the same age, of which six are female all six pounds below the normal for the age, as judged by Holt's figures for female children at that age, and four are males, all two pounds underweight, as judged from the figures for male children, the figure on the graph for variation from normal would be $\frac{4+6}{10} = 4.44$ pounds, below normal, which is represented as a single point on the graph.

It will be noted from table 1 that there is a difference in the age distribution of the two series. In the premature series the largest number of cases falls into the first three age groups one to two, two to three, three to four, giving a total

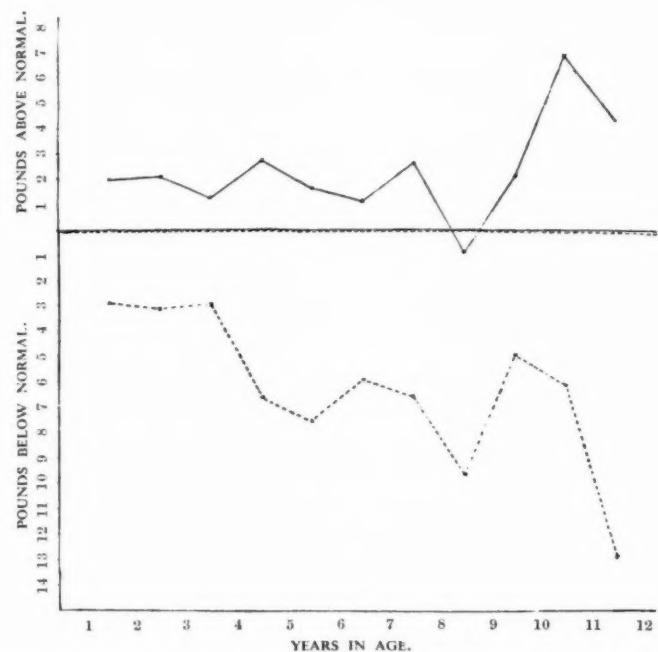


FIG. 1. Graph showing mean variation from normal (using Holt's figures) of children of both sexes, from the age of 1 to 12 which (1) weighed 8½ lb. or more at birth, (2) weighed 5½ lb. or under at birth.

— children which weighed 8½ lb. or more at birth.
- - - children which weighed 5½ lb. or less at birth.
- - - normal weight for appropriate age and sex.

of sixty-two cases, whereas in the control series there are only thirty-five cases in these age groups : in the control group the largest number falls into the age period of five to eight, with a total of sixty-four cases, as compared with a total of thirty-nine in the same group of the premature series. The significance of this difference is not easy to understand, but may lie in a greater delicacy of the prematurely born child in the earlier years of childhood. A study of incidence of infectious fevers in the two series, however, does not support this idea. Certain other records of the two series of cases were kept, and these are included in the tables.

TABLE I
EFFECT OF BIRTH WEIGHT ON WEIGHT LATER IN CHILDHOOD
TABLE 1A. VARIATION FROM NORMAL WEIGHT OF CHILDREN WHICH AT BIRTH WEIGHED LESS THAN $5\frac{1}{2}$ LB.

AGE	NUMBER OF CASES	WEIGHT NORMAL OR 0-5 LB. ABOVE NORMAL	5-10 LB. ABOVE NORMAL	10-20 LB. ABOVE NORMAL	MORE THAN 20 LB. ABOVE NORMAL		WEIGHT SUB-NORMAL 0-5 LB. BELOW NORMAL	5-10 LB. BELOW NORMAL	10-20 LB. BELOW NORMAL	MORE THAN 20 LB. BELOW NORMAL
1-2	17	2	0	0	0		12	3	0	0
2-3	21	4	0	0	0		12	2	3	0
3-4	24	7	0	0	0		9	7	1	0
4-5	12	1	0	0	0		4	3	4	0
5-6	17	0	0	0	0		3	11	3	0
6-7	16	2	0	0	0		4	6	4	0
7-8	6	0	1	0	0		2	2	0	1
8-9	13	1	0	0	0		3	2	6	1
9-10	9	2	0	0	0		2	4	1	0
10-11	6	1	0	0	0		2	1	2	0
11-12	9	0	0	0	0		0	3	4	2
TOTAL	150	20	1	0	0		53	44	28	4

TABLE 1B. VARIATION FROM NORMAL WEIGHT OF CHILDREN WHICH AT BIRTH WEIGHED MORE THAN $5\frac{1}{2}$ LB.

AGE	NUMBER OF CASES	WEIGHT NORMAL OR 0-5 LB. ABOVE NORMAL	5-10 LB. ABOVE NORMAL	10-20 LB. ABOVE NORMAL	MORE THAN 20 LB. ABOVE NORMAL		WEIGHT SUB-NORMAL 0-5 LB. BELOW NORMAL	5-10 LB. BELOW NORMAL	10-20 LB. BELOW NORMAL	MORE THAN 20 LB. BELOW NORMAL
1-2	9	7	1	0	0		0	1	0	0
2-3	13	10	1	0	0		0	2	0	0
3-4	13	7	2	0	0		0	4	0	0
4-5	11	5	4	0	0		0	1	1	0
5-6	22	10	1	2	1		0	5	3	0
6-7	23	8	2	3	0		0	8	2	0
7-8	18	4	4	1	2		0	3	4	0
8-9	16	6	1	1	0		0	3	5	0
9-10	6	1	1	1	0		0	2	1	0
10-11	12	4	2	1	1		0	2	1	0
11-12	7	1	1	1	1		1	1	1	2
TOTAL	150	63	20	10	6		31	18	2	0

1. The effect of birth weight on the weight in later childhood

Fig. 1 shows at a glance that the prematurely born child, that is the child weighing five and a half pounds or less at birth, weighs on the average far less throughout childhood than the child weighing eight and a half pounds or more at birth. Irregularities in the curve are inevitable in a small series and are readily understood when reference is made to table 1, based on a table from which the graph was prepared. It will be seen that the reason for the fact that the curve for the control group at one point drops below normal is due chiefly to the fact that in the age group of 8-9 there happen to be five children weighing from five to ten pounds below normal—a higher figure than in any other age group of the series. These irregularities would disappear in a larger series.

Table 2 is a summary of table 1.

TABLE 2
EFFECT OF BIRTH WEIGHT ON SUBSEQUENT WEIGHT

IN THE PREMATURE SERIES				CONTROL SERIES (OVER 8½ LB. AT BIRTH)		
Normal or overweight	21	14 per cent.		99	66	per cent.
Underweight	129	86 per cent.		51	34	per cent.
More than 5 lb. overweight	1	0·66 per cent.		36	24	per cent.
" " 5 lb. underweight	76	50·66 per cent.		20	13·3	per cent.
" " 10 lb. underweight	32	21·33 per cent.		2	1·33	per cent.

The points to note are that eighty-six per cent. of all premature children in the series of a hundred and fifty cases are underweight at the various ages seen : that only one child in this series falls into the five pounds or more overweight group—and this child was actually five pounds above the normal for the age : and the most important point of all is to note how many grossly underweight children there are in the premature series—21·33 per cent. being more than ten pounds underweight compared with 1·33 per cent. in the control group. These children are in actual fact dwarfed, and prematurity can be seen to be a very common cause of dwarfism.

It is regretted that the heights of the children were not taken regularly. Owing to paucity of records of heights it is not proposed to present the figures—which only cover 35 per cent. of the children studied : but it can be stated that the heights of the children in the premature series were considerably less than the heights of those in the control group—and this tallies with the more careful study of Hess (1934) on the subject.

Table 3 is merely a further explanation of the graph and shows the mean difference in the weight of the premature baby in later childhood compared with that of the child which at birth weighed eight and a half pounds or over.

When it is seen that in a series of three hundred cases the mean difference in weight between the two groups varies from 4·2 to 17·1 pounds, it will be realized that if these figures are confirmed by subsequent workers, all weight charts which attempt to give a range of normality for children are of no use at all as a comparison for any individual case unless they take into account the weight of the children at birth.

An analysis of the smaller variations of birth weight within the two series was made to decide whether with the limited numbers available it could be demonstrated that the smaller variations in birth weight also showed a demonstrable difference in the weight in later childhood. The figures are presented for what they are worth, but the series is too small to be of any real value in this connexion.

TABLE 3
EFFECT OF BIRTH WEIGHT ON SUBSEQUENT WEIGHT

MEAN DIFFERENCE IN WEIGHT BETWEEN CHILDREN IN THE PREMATURE SERIES AND THE CONTROL SERIES AT THE VARIOUS AGE PERIODS

AGE (YEARS)	MEAN DIFFERENCE (POUNDS)	TOTAL CASES ON WHICH FIGURES ARE BASED
1-2	4·9	26
2-3	5·2	34
3-4	4·2	37
4-5	9·4	23
5-6	9·2	39
6-7	7·1	39
7-8	9·2	24
8-9	8·8	29
9-10	7·0	15
10-11	13·0	18
11-12	17·1	16
		300

Tables 4 and 5 give the analysis of the relevant figures in the premature series, and table 6 the relevant figures in the control series.

TABLE 4
EFFECT OF BIRTH WEIGHT ON SUBSEQUENT WEIGHT

BIRTH WEIGHT OF CHILDREN IN THE PREMATURE SERIES WHICH WERE MORE THAN 10 LB.
UNDERWEIGHT

TOTAL 32 CASES. Birth weight 4-5½ lb. 26 cases 81·2 per cent.
Less than 4 lb. 6 cases 18·8 per cent.

Compare with 21 cases in the premature series now of normal weight or above
normal weight :

Birth weight 4-5½ lb. 17 cases 80·9 per cent.
Less than 4 lb. 4 cases 19·1 per cent.

TABLE 5
EFFECT OF BIRTH WEIGHT ON SUBSEQUENT WEIGHT

STUDY OF THE PRESENT WEIGHT OF THOSE WHICH WERE UNDER 4 LB. AT BIRTH, COMPARED WITH THOSE WHICH WEIGHED OVER 4 LB. AT BIRTH. (PREMATURE SERIES ONLY)

Total cases weighing 4-5½ lb. at birth 312 cases
 Total cases weighing under 4 lb. at birth 27 cases
 Of those weighing under 4 lb. at birth (27 cases)

Now normal weight or above normal	4	14·9 per cent.
0-5 lb. underweight	7	25·9 per cent.
5-10 lb. underweight	12	44·4 per cent.
More than 10 lb. underweight	4	14·8 per cent.

Those weighing over 4-5½ lb. at birth (123 cases)

Now normal or above normal	17	13·8 per cent.
0-5 lb. underweight	46	37·3 per cent.
5-10 lb. underweight	32	26·0 per cent.
More than 10 lb. underweight	28	22·9 per cent.

One might point out that of those weighing under four pounds at birth 59·2 per cent. are five or more pounds underweight later : of those weighing four to five and a half pounds at birth 48·9 per cent. are five or more pounds underweight when examined. The lowest birth weight was one pound eight ounces.

TABLE 6
EFFECT OF BIRTH WEIGHT ON SUBSEQUENT WEIGHT

WEIGHT OF BABIES OVER 10 LB. AT BIRTH COMPARED WITH WEIGHT OF THOSE WEIGHING 8½-10 LB. AT BIRTH

OVER 10 LB. AT BIRTH (24 CASES)			OTHERS (126). BIRTH WEIGHT 8½-10 LB.	
More than 10 lb. underweight	0	2 1·6 per cent.
5-10 lb. underweight	4 16·7 per cent.	14 11·1 per cent.
0-5 lb. underweight	5 20·8 per cent.	26 20·7 per cent.
Normal or up to 5 lb. overweight	10 41·6 per cent.	53 42·1 per cent.
5-10 lb. overweight	1 4·2 per cent.	19 15·1 per cent.
10-20 lb. overweight	4 16·7 per cent.	6 4·7 per cent.
20 lb. overweight	0	6 4·7 per cent.

2. Effect of breast feeding on subsequent weight

Tables 7-10 show the effect of breast feeding in infancy on the weight in later childhood.

TABLE 7
EFFECT OF BREAST FEEDING ON WEIGHT (I)

Of those children which are more than 10 lb. underweight (32 cases) in the premature series :

Breast fed less than 2 months	16	50 per cent.
2-6 months	10	31·2 per cent.
6-9 months	6	18·8 per cent.

Total prematures not breast fed for 2 months, 60.

Compare with 21 cases in the premature series which are of normal weight or over :

Breast fed less than 2 months	9	42·8 per cent.
2-6 months	7	33·3 per cent.
6-9 months	5	23·9 per cent.

TABLE 8
EFFECT OF BREAST FEEDING ON WEIGHT (II)

PRESENT WEIGHT OF CHILDREN IN PREMATURE SERIES NOT BREAST FED FOR 2 MONTHS.
(TOTAL 60)

More than 20 lb. underweight	2	3·33 per cent.
10-20 lb. underweight	14	23·33 per cent.
5-10 lb. underweight	15	25·00 per cent.
0-5 lb. underweight	20	33·33 per cent.
Normal or up to 5 lb. over	9	15·00 per cent.
More than 5 lb. over	0	

PRESENT WEIGHT OF CHILDREN IN PREMATURE SERIES BREAST FED FOR 6 MONTHS OR MORE
(TOTAL 52)

More than 20 lb. underweight	2	3·8 per cent.
10-20 lb. underweight	6	11·6 per cent.
5-10 lb. underweight	16	30·8 per cent.
0-5 lb. underweight	22	42·3 per cent.
Normal or up to 5 lb. over	5	9·6 per cent.
5-10 lb. over	1	1·9 per cent.
More than 10 lb. over	0	

TABLE 9
EFFECT OF BREAST FEEDING ON WEIGHT (III)

DURATION OF BREAST FEEDING IN THOSE OF THE CONTROL SERIES WHICH ARE UNDERWEIGHT.
(TOTAL 49)

(No mention of duration of breast feeding made in two cases
in the series now underweight)

Not breast fed for 2 months	17	34·7 per cent.
2-6 months	12	24·5 per cent.
6 months or over	20	40·8 per cent.

TABLE 9—continued
EFFECT OF BREAST FEEDING ON WEIGHT (III)

DURATION OF BREAST FEEDING IN THE CONTROLS NOW OF NORMAL WEIGHT (TOTAL 99)

Breast fed less than 2 months	27	27·28 per cent.
2-6 months	11	11·11 per cent.
6 months or more	61	61·61 per cent.

TABLE 10
EFFECT OF BREAST FEEDING ON WEIGHT (IV)

WEIGHTS OF THOSE IN THE CONTROL SERIES NOT BREAST FED FOR 2 MONTHS COMPARED
WITH THOSE FED 6 MONTHS OR MORE ON THE BREAST

44 controls not breast fed for 2 months

5-10 lb. underweight	7	15·91 per cent.
0-5 lb. underweight	9	20·45 per cent.
Normal or overweight	28	63·64 per cent.

80 controls breast fed for 6 months or more

5-20 lb. underweight	9	11·2 per cent.
0-5 lb. underweight	12	15·0 per cent.
Normal or overweight	59	73·8 per cent.

The numbers when divided into groups are small, but table 7 seems to indicate that breast feeding in infancy has some effect on the weight in later childhood and table 10 tends to confirm it. It will be seen that 25·66 per cent. of those infants in the premature series not breast-fed for two months are more than ten pounds under weight, and that only 15·4 per cent. of those fed on the breast for longer than six months are more than ten pounds underweight. It must be remembered that this difference may be due in part to variations in the birth weight, because a very small baby at birth is less likely to be breast-fed than a baby larger at birth. Tables 9 and 10, which are based on a similar analysis of the control group, confirm the suggestion that breast feeding in infancy has some effect on the ultimate weight of the child.

3. Incidence of infectious diseases in two series

Table 11 was compiled to determine if it was true, as it is often stated, that the premature child is more delicate and more liable to infection in later childhood than the child of normal weight at birth. It might be expected that this would be the case, as it would be reasonable to suppose that the small underweight child would have less resistance than the larger overweight child. For this purpose the incidence of infectious fevers in two age groups is given, the first two to four years and the second nine to twelve years. It will be seen that there is no difference between the two groups. This is in accordance with the finding of Hess in his series.

TABLE 11

INCIDENCE OF INFECTIOUS DISEASES IN PREMATURE SERIES COMPARED WITH THAT IN CONTROL SERIES

Two age groups used: 2-4 years and 9-12 years.

PREMATURES		CONTROLS	
Age 2-4 31 cases with record		20 cases with record	
Number who had not had fever ..	13 (41.9 per cent.)	Number who had had no fever ..	8 (40 per cent.)
who had had		who had had	Measles 4
Measles	8	Chicken pox	2
Chicken pox	3	Scarlet fever	0
Scarlet fever	2	Diphtheria	0
Diphtheria	1	Whooping cough	6
Whooping cough	6	Mumps	2
Mumps	1	Rubella	1
Rubella	4		
Age 9-12 20 cases with record		22 cases with record	
Number who had not had any fever ..	0	Number who had not had any fever ..	0
who had had		who had had	Measles 19
Measles	19	Chicken pox	14
Chicken pox	10	Scarlet fever	2
Scarlet fever	5	Diphtheria	3
Diphtheria	5	Whooping cough	14
Whooping cough	11	Mumps	10
Mumps	10	Rubella	5
Rubella	1		

4. Sex incidence in the two groups

TABLE 12

SEX INCIDENCE IN PREMATURE AND CONTROL SERIES

PREMATURES		CONTROLS			
Males	79	52.6 per cent.	Males	107	71.3 per cent.
Females	71	47.4 per cent.	Females	43	28.7 per cent.
Cases 10 lb. or more underweight					
PREMATURES		CONTROLS			
Males	15	46.9 per cent.	Males	2	
Females	17	53.1 per cent.	Females	0	
Cases 10 lb. or more overweight					
PREMATURES		CONTROLS			
Males	0	Males	5		
Females	0	Females	11		

The difference in the sex incidence of the two groups is difficult to understand. It is to be noted that in the premature series fewer males are more than ten pounds underweight than females, while in the control group more females are more than ten pounds overweight than males. This again is one of the points which only a much larger series could make clear.

5. Incidence of epilepsy and gross cerebral defect in the two series

The following is an analysis of the incidence of the above conditions in the two series :

TABLE 13

INCIDENCE OF SPASTICITY, MENTAL DEFICIENCY, CONVULSIONS AND ATHETOSIS IN THE TWO SERIES

PREMATURES	CONTROLS
Spastic diplegia 12 (8 per cent.)	1, not forceps delivery No maternal toxæmia
Spasticity alone 7	
With gross mental deficiency 3	1
With fits 1	
With athetosis 1	
Total 12	Total 1.
Gross mental deficiency 14 (9.33 per cent.)	2, one breech delivery. No maternal toxæmia
Mongol 1	
With fits 2	
With spasticity 3	
Others 8	
Total 14	Total 2, as above.
Convulsions 9 (6 per cent.) (Other than neonatal)	7, all non-instrumental deliveries. No maternal toxæmia
True epilepsy 5	6
Fits with mental defect 1	1
Salaams 2	
Fits with spasticity 1	
Total 9	Total 7
Athetosis 2	0
Alone 1	
With spasticity 1	
Total 2	
Total cases with spasticity,	
Mental defects, fits or athetosis 30 (20 per cent.)	10 6.66 per cent.
Above cases excluding epilepsy and salaams without mental defect 24	4

Only cases of gross mental defect were included in the above series. Any case in which the mental defect was not gross, or in which, for instance, the child was merely backward at school and to an observer in the out-patient department appeared to be normal, was not included in the series.

A further analysis of the relation of birth weight to the above conditions is given in table 14.

TABLE 14
RELATION OF BIRTH WEIGHT TO ABOVE CONDITIONS

OF 27 CASES UNDER 4 LB. AT BIRTH :

- 3 are spastic alone,
- 2 are spastic and mentally defective
- 4 are grossly mentally defective without spasticity,
- 1 is spastic and has athetosis,
- 1 has athetosis alone.

Total : 11 with severe cerebral damage (40.7 per cent.). None has fits.

OF 123 CASES WEIGHING 4-5½ LB. AT BIRTH :

- 13 cases (10.5 per cent.) have the above conditions of severe cerebral damage or agenesis.

To put it in another way, of twenty-eight cases of severe cerebral damage or agenesis in the combined series of three hundred cases (excluding epilepsy) :

- 16 (57.1 per cent.) are more than 1 month premature.
- 11 (39.2 per cent.) weighed under 4 lb. at birth.
- 13 (46.4 per cent.) weighed 4-5½ lb. at birth.
- 4 (14.4 per cent.) weighed over 8½ lb. at birth.

In one case only was there a history of maternal toxæmia (taken as renal trouble apart from pyelitis associated with oedema of the legs) : the one case in which there was such a history had spasticity with mental deficiency. Maternal toxæmia was noted in a total of twenty-six cases in the combined series of three hundred.

Table 15 is a study of the weight of children with spastic diplegia in the two series.

TABLE 15
WEIGHT OF THE 13 CASES OF SPASTIC DIPLEGIA IN COMBINED SERIES

Normal or overweight	2
Less than 5 lb. underweight	3
5-10 lb. underweight	7
More than 10 lb. underweight	1

6. Incidence of asthma and eczema in the two series

It was noted on looking through the diagnoses of the cases in the two series that there were many cases of asthma in the control group and few in the premature group. On counting these up it was found that of thirty cases of asthma in the combined series of three hundred cases, twenty-seven or ninety per cent. were in the control group, there being only three cases in the premature series.

In order to follow this point up an analysis was made of the birth weight of a hundred and fifty consecutive cases of asthma and fifty consecutive cases of infantile eczema seen at the hospital in the last two years, and for comparison the birth weight of two hundred consecutive children attending the out-patient department for complaints other than asthma and eczema was recorded. The results are shown in table 16.

TABLE 16

BIRTH WEIGHT OF 200 ALLERGIC CASES COMPARED WITH THAT OF 200 CONTROLS

BIRTH WEIGHT	ASTHMA (150 CASES)	ECZEMA (50 CASES)	TOTAL ALLERGY (200 CASES)	CONTROLS (200 CASES)
Under 5 lb.	6 4 per cent.	1 2 per cent.	7 3.5 per cent.	19 9.5 per cent.
5½-7 lb. ..	21 14 per cent.	9 18 per cent.	30 15 per cent.	72 36 per cent.
7-8 lb. ..	55 36.7 per cent.	13 26 per cent.	68 34 per cent.	69 34.5 per cent.
Over 8 lb. ..	68 45.3 per cent.	27 54 per cent.	95 47.5 per cent.	40 20 per cent.

The table shows at a glance that the heavy baby at birth is very much more liable to be allergic than the small baby. The reason for this at the moment does not appear clear.

Discussion

The figures given in this communication suggest that the weight of the pre-school and the school-child is greatly influenced by the birth weight, and the effect of the birth weight on subsequent weight is so great that every weight chart which attempts to give a range of normality for children should take this factor into account. It seems reasonable to suggest that those who study the weight and height of children should go even further back than the birth weight to the factors which affect the weight at birth—factors racial, hereditary, environmental and pathological in the mother, possibly to pathological conditions of the foetus.

Several authors have suggested that there is a relationship between the mother's state of nutrition in pregnancy and the weight of the new-born infant.

Sison and Calang (1931), working among Filipino women, demonstrated the connexion between financial status, the nutritional condition of the mother and the weight of the child at birth : the average birth weight of the child born of the well nourished mother was more than 300 grammes greater than that of the child born of the ill-nourished woman. E. V. Davis (1928) in America is so convinced of the effect of the diet of the mother in pregnancy on the ultimate weight of the child at birth that she prescribes a special diet as an obstetrical measure to keep down the size of the foetus and so make delivery easy. Letournier as far back as 1897 showed that mothers with heavy occupations bore children which weighed considerably less than those born to mothers who had light occupations. Matthews Duncan (1866) showed the effect of the age of the mother on the birth weight of the foetus, and Ingerslev (1876) demonstrated the difference in the birth weight of foetuses born from multiparous and primiparous women.

Many other factors have been stated to influence the birth weight, and if the birth weight has as great an influence on the weight in subsequent childhood as the figures in this communication suggest, it will be seen that quite remote factors may have a considerable ultimate effect on the weight and height of children. One possibility, however, must be mentioned. The failure of the premature baby to gain weight in infancy and in later childhood may be due to inadequate feeding in the early weeks of life. The premature babies studied by Hess (1934) in America apparently caught up to their full term siblings in weight and height after four years, and it is possible that this is due to the special care which the children received in Hess's clinic from the earliest days onward. The children whose weights were used for the present study had had no such special care : it is true that a number had been attending Maternity and Child Welfare Centres and School Clinics, but it is certain that a minority of the children in the series received in infancy the care given to children in the American series.

Summary

The after-history of a hundred and fifty children who weighed five and a half pounds or less at birth is compared with that of a hundred and fifty children who weighed eight and a half pounds or more at birth. The children were taken consecutively irrespective of diagnosis. It is found that :

1. 86 per cent. of the premature series at the various ages of childhood are underweight, using Holt's figures as a standard, whereas only 34 per cent. of the control series are underweight.

2. 21·33 per cent. of the premature series are more than ten pounds underweight, compared with 1·33 per cent. in the control group.

3. 0·66 per cent. of the premature series are five pounds overweight and none more than five pounds overweight. 24 per cent. of the control series are more than five pounds above the average weight for the age.

4. The mean difference between the weight of the two groups at the various ages varies from 4·2 pounds to 17·1 pounds, with a tendency to increase as age increases.

5. Prematurity at birth is presented as a common cause of dwarfism in children.

6. The duration of breast feeding appeared to have some effect on the ultimate weight of the child, those breast fed more than six months appearing to weigh more later than those breast fed for less than two months.

7. There was no difference in the incidence of infectious diseases in the two groups.

8. The sex incidence in the two groups is discussed.

9. The high incidence of spasticity and other cerebral defects in the premature group is discussed and analysed.

10. The fact that the premature or small baby is less likely to be an allergic subject than the baby large at birth is shown by figures given. 54 per cent. of children with infantile eczema weighed more than eight pounds at birth compared with 20 per cent. of a control series of children attending the out-patient department for other complaints.

11. It is suggested that the weight of the pre-school and the school child may well depend on factors quite remote—the financial status of the mother, the diet she takes in pregnancy, the occupation of the mother, hereditary factors and pathological conditions of the mother.

The paper is based on a small series of cases but it is hoped that others who have access to a large series of figures such as Maternity and Child Welfare Officers and School Medical Officers will supplement these results in order to show whether or not they are applicable in general.

Thanks are due to the entire Honorary Staff of the Hospital for Sick Children for permission to publish details of their cases, and to Dr. W. J. Martin, of the London School of Hygiene and Tropical Medicine, for advice on the presentation of the statistics.

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THE ULTIMATE PROGNOSIS OF NEPHRITIS IN CHILDHOOD

TOGETHER WITH A STUDY OF THE INCIDENCE OF ANAEMIA
IN THE VARIOUS STAGES OF THE DISEASE

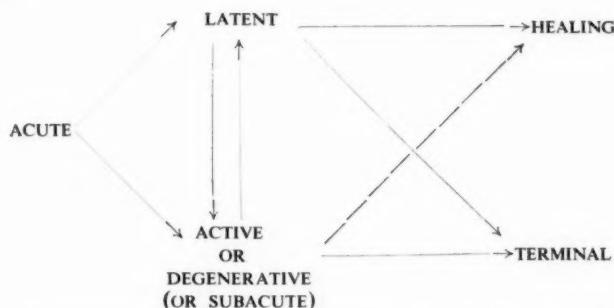
BY

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The ultimate prognosis of acute nephritis in children has always been a subject of interest to the paediatrician. The relative frequency of acute nephritis in childhood and the fact that many cases of renal failure in adult life cannot be explained, have led to repeated attempts to correlate the childhood illness with the adult renal failure. Until recent years and with traditional methods of examination these efforts have failed, but Addis (1925) gave clinicians a sign by which they can distinguish between those children who have fully recovered from acute nephritis and those who appear equally healthy, but are actually in the latent stage of nephritis, and will ultimately die of renal failure or its complications.

After many years' work he devised a method by which a quantitative estimation can be made of the urinary protein and the cellular elements in the sediment and gave the upper limits of normal in adults and the conditions under which reliable results can be obtained. By using this method he had followed cases of Bright's disease from the acute stage through the latent stage in which they were apparently normal, although quantitative examination of their urine showed that the renal lesion was still active, and through the active or subacute stage to the terminal stage of chronic nephritis. In this way he established the connection between acute nephritis in childhood and degenerative or chronic nephritis in adult life. He suggested the following diagram as depicting the course of nephritis :



* In receipt of a grant from the Medical Research Council.

Since that time various workers (Lytle, 1933 ; Snoise, 1938) have applied Addis's method to the examination of the urine of children and established the upper limits of normal for albumin and cellular elements. Their results are all very similar. Those given by Snoise are reproduced here since they have been used in the present series of cases.

**CELLULAR ELEMENTS AND PROTEIN IN TWELVE HOURS NIGHT
URINE IN NORMAL CHILDREN (SNOKE)**

RANGE	MEAN VALUE	STANDARD DEVIATION	
Casts 0-29000	1230	3900	95 per cent. under 9000. All were hyaline or granular.
R.B.C. 0-800000	8600	116300	Above 600000 suspicious.
Protein 5-90 mgm.	28.5 mgm.	13.2 mgm.	95 per cent. under 55 mgm. 55 mgm. suggested as upper limit of normal.

Scope of enquiry

For the purpose of this investigation, all the children who had been in the general wards of this hospital with nephritis at any stage of the disease since 1934 and a few unselected cases from 1933 were requested to report to the hospital. Out of a hundred and forty-eight such cases, a hundred and twenty (eighty-one per cent.) reported. These were subjected to a general clinical examination, including measurement of blood pressure, and the mother was given typed instructions for the collection of a twelve hours' specimen of urine for examination by the Addis method.

The albuminuria was estimated by the Kjeldahl method since it had been found in the examination of the urine in cases of acute haemorrhagic nephritis with gross haematuria and albuminuria that the method of Shevky and Stafford as modified (Peters and Van Slyke, 1932) and used by Addis and Snoise, gave results which were considerably higher than those given by the Kjeldahl method. In any case in which the albuminuria was near the upper limit of normal it was estimated by both methods and the results obtained by the method of Stafford and Shevky were accepted in order that the results should be comparable with those of Snoise and other workers. At least two specimens were examined. The urines were usually satisfactory as regards volume, specific gravity (above 1020) and acidity to litmus. If two such specimens could not be collected at home, either the child was admitted to the ward for twenty-four hours or the case was discarded. If the first showed an obvious abnormality, a second specimen was not always examined. If one specimen was normal and one was abnormal, the renal lesion was considered to be active at the time of the abnormal specimen. If either specimen was suspicious, further examinations were made, if possible, until a definitely abnormal result was obtained. It is possible that the number of cases that were actually in the latent stage was higher than the figures show, as Snoise considers that consistently normal results over at least a year are necessary before the child can be regarded as cured. No result was considered abnormal because of an excess of white blood cells, epithelial cells or casts alone. The majority of cases in the latent stage excreted an excess of red blood corpuscles, a few had albuminuria and haematuria, and a few had albuminuria only. I can confirm Snoise's statement

that in the presence of heavy albuminuria it may be difficult to detect haematuria, and repeated examinations may be necessary before an abnormal count is obtained.

When the urine was found to be abnormal or suspicious, the blood non-protein nitrogen or urea was estimated whenever possible. If the urine was abnormal, but both the blood pressure and non-protein nitrogen were normal, the child was considered to be in the latent stage. If the urine and either the blood pressure or the non-protein nitrogen were abnormal, the child was considered to be in the terminal stage. Only those children who were constantly or frequently in a state of generalized oedema were considered to be in the active stage. The plasma proteins were estimated by the method of Folin and Wu in as many cases as possible.

Clinical features

The latent stage was in most cases characterized by good health and freedom from symptoms, but in a few cases the mother reported that the child's face occasionally became puffy with a cold. Of thirty-eight cases in the latent stage, only five had any subjective symptoms referable to renal disease. Of these, four were known to have had renal disease for more than two years and one for one year and ten months, so that it is possible that they were all passing into the terminal stage of renal failure. These five children, together with five out of six who were found to be in the terminal stage complained of recurrent attacks of headache, nausea and vomiting in the mornings. The attacks varied in frequency from once weekly to once in several months. In some cases they were migrainous in character and when the vomiting was over the child felt perfectly well and attended school in the afternoon.

None of the children in the terminal stage was free from symptoms. Five suffered from recurrent attacks of morning vomiting and headache, two complained of tiredness which was worst in the mornings, and one had recurrent abdominal pain without vomiting. All except one, however, were attending school, and this one had severe renal failure which caused her death eight weeks after the onset of symptoms.

The four children who were in the active stage were all oedematous either constantly or with short periods of freedom. Three were free from symptoms apart from the oedema, and the remaining case, who was approaching renal failure, complained of headaches and lassitude in the mornings.

These findings confirm the general impression that in children with chronic nephritis, subjective ill health does not occur until renal failure is advanced. It is therefore not advisable to place much reliance on the presence or absence of symptoms in assessing the state of the kidneys.

Results and discussion

The plasma proteins in the various stages of nephritis.

The plasma proteins were estimated by the method of Folin and Wu in as many cases as possible. The results were as follows :

TYPE OF CASE	NO. OF CASES	PLASMA ALBUMIN (GM. PER CENT.)		PLASMA GLOBULIN (GM. PER CENT.)		TOTAL PROTEIN (GM. PER CENT.)	
		RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE
Healed or normal control	5	3.10-4.4	3.68	2.52-3.28	2.81	5.87-7.58	6.58
Latent ..	16	1.95-4.23	3.12	1.56-3.34	2.57	4.30-6.90	5.70
Active ..	4	1.47-2.82	1.91	1.51-2.94	1.97	2.98-4.71	3.88
Terminal ..	8	1.82-3.8	3.25	1.44-2.71	2.07	4.14-6.28	5.29

The values for the plasma albumin in the healed and normal cases are slightly below the values given as normal by Rappaport (1935). It is possible that the plasma albumin is easily and frequently depressed in children, especially when the diet is low in first-class protein, as it is in most working-class children.

One child who had completely recovered from acute nephritis was interesting in this respect. On first examination of his blood the following results were obtained—plasma albumin 3.55 gm. per cent., plasma globulin 4.17 gm. per cent., total protein 7.58 gm. per cent. It was found that the child had been on a low protein diet for the three years which had elapsed since his attack of acute glomerular nephritis. The mother was therefore instructed to give him a full diet with one pint of milk and meat or fish daily for six weeks, at the end of which time his blood was re-examined with the following results—plasma albumin 4.4 gm. per cent., plasma globulin 2.52 gm. per cent., total protein 6.92 gm. per cent., showing a rise in plasma albumin and a fall in the globulin.

In the majority of cases in which dietary restrictions had been continued for a long time after the recovery from nephritis, only red meat and occasionally eggs had been withheld, so that close questioning showed that the child had been receiving the usual amount of protein for his age and social position. This case indicates the possible ill-effects of severe dietary restriction even when there is no loss of albumin by albuminuria. In the latent stage about half the cases had plasma proteins within the range shown by the normal cases, and all the cases in which the total proteins were greatly reduced showed persistent albuminuria. All the cases in the active stage showed greatly reduced plasma albumin and total plasma protein values, which is consistent with the heavy albuminuria and oedema found in these cases. This is the only stage of the disease in which a typical and gross deviation from normal was constant. In the terminal stage all except one case had normal plasma albumin, four out of the eight cases examined had normal total protein. The only case with greatly reduced plasma albumin and total protein had persistent heavy albuminuria and occasional slight oedema for several months at least, but was grouped with those in the terminal stage because of nitrogen and phosphorus retention. The absence of correlation between the level of plasma proteins and the occurrence of oedema was striking in some cases, the critical level of total plasma proteins at which oedema developed apparently being between 4.0 gm. per cent. and 5.0 gm. per cent. in most cases. That some other factor must be involved is shown by the following cases which were examined on different

occasions so that values were obtained when oedema was present and when they were free from oedema.

CASE	OEDEMA PRESENT			OEDEMA ABSENT		
	PLASMA ALBUMIN (GM. PER CENT.)	PLASMA GLOBULIN (GM. PER CENT.)	TOTAL PROTEIN (GM. PER CENT.)	PLASMA ALBUMIN (GM. PER CENT.)	PLASMA GLOBULIN (GM. PER CENT.)	TOTAL PROTEIN (GM. PER CENT.)
O.K.	2.0	1.96	3.96	1.82	2.32	4.14
R.T.	1.47	1.51	3.98	1.80	4.04	5.84
G.D.	2.82	1.53	4.35	3.00	2.20	5.20
C.A.	1.77	2.94	4.71	1.55	2.55	4.10
C.C.	0.75	2.94	3.69	2.20	2.10	4.30

1. Cases with acute haemorrhagic nephritis at onset.—A hundred and two cases of acute haemorrhagic nephritis have been studied. Of these nine died during the acute stage of various septic complications and not primarily of nephritis. They were therefore discarded. Another five were examined, but satisfactory specimens could not be obtained and they were discarded. Eighty-eight cases remained. Of these three died in the acute stage. Two cases were found to be in the terminal stage with hypertension or nitrogen retention. No case was found to be in, or to have passed through, the active or subacute stage. The remaining cases were examined six months to six years after the onset with the following results :

TIME AFTER ONSET	½-1 YR.	1-2 YR.	2-3 YR.	3-4 YR.	4-5 YR.	5-6 YR.
Healed .. .	5*	12†	13‡	10	12	4
Latent .. .	2	14	3	4	2	2
Percentage of total which were healed	70	46	81	71	86	68

In the first two years the percentage of the total which were healed was 51.5. After the first two years the percentage of the total which were healed was 75. It will be seen that after the first two years from the onset the percentage of healed cases does not rise, which supports the statements of K. de Leeuw (1937) and Snoke (1937) that healing rarely occurs, if it has not already done so, after the first two years. Of all the cases seen two years or more after the onset, seventy-five per cent. are healed. It is probable that none of the cases which are in the latent stage two years or more after the onset and only seventy-five per cent. of the cases in the first two years will recover. Of the total eighty-eight cases, the results are as follows :

DEAD IN ACUTE STAGE—3 cases	3.4 per cent.
IN TERMINAL STAGE—2 cases	2.3 per cent.
IN LATENT STAGE—28 cases	32 per cent.
HEALED—56 cases	64 per cent.
ESTIMATED TOTAL ULTIMATE MORTALITY	27 per cent.

* 2 suspicious

† 2 suspicious

‡ 1 suspicious.

Previous investigators have given varying reports on the ultimate prognosis in this condition, the severity of the prognosis given largely depending on the methods used to determine whether or not complete healing of the renal condition had occurred. Smellie (1926) reviewed nine cases of acute nephritis six months to eight years after the onset, and found that one had died, apparently of an acute exacerbation of the initial attack, seven appeared normal (77·7 per cent.), and one was apparently in the chronic stage, although the urine was normal. Of thirty-nine cases he reviewed at an average time of sixteen years after the onset, all were symptomatically well. Sixteen were examined. Of these eleven had either raised blood urea and low urea concentration tests or enlarged hearts and raised blood pressure, but it was difficult to assess the significance of these findings in view of the normal urinary findings. Smellie came to the conclusion that the ultimate prognosis in acute nephritis was good when the treatment of the initial attack was efficient, and that the cases of renal failure in adult life were accounted for by subclinical and therefore untreated attacks in childhood. Lyttle and Rosenberg (1929) reported the results of observations on ninety-nine cases which had been followed for several years after the onset of acute nephritis. They were observed in the out-patient department, and regular clinical and routine urine examinations were made. Of seventy-four cases of acute glomerular nephritis, the immediate mortality was 5·4 per cent. and 5·4 per cent. of the cases became chronic. The remaining 89·2 per cent. appeared to be in good health. K. de Leeuw (1937) reported his findings in eighty cases of nephritis which had been seen in the previous seventeen years. Of sixty-nine with an observed initial attack of acute glomerular nephritis, sixty-three or ninety-one per cent. had completely recovered, but a few of these showed 'negligible quantities of albumin or sporadic red blood corpuscles' in the urine, which findings were not considered abnormal. Only one had chronic nephritis, one had orthostatic albuminuria, and one had some form of chronic renal infection. In all these investigations the percentage of cases of acute nephritis which appeared to become chronic was small, and apparently complete recovery occurred in ninety per cent. of the cases in the series of K. de Leeuw and Lyttle and Rosenberg.

Two series of cases have been reported in which the Addis method has been used for the assessment of recovery. Boyle et al. (1937) reported on a series of twenty-five cases which were clinically recovered from acute post-infectious nephritis six months to eight years after the onset. The cases were selected from a series of two hundred and fifty such cases in order to include more than the correct percentage of severe initial attacks with acute cerebral manifestations or prolonged albuminuria. The urine of each case was examined once by the Addis technique. All except one of the cases gave results within the upper limit of normal as defined by Lyttle for children, and the remaining case was found to have a chronic infection of the renal tract. The authors concluded that children who have clinically recovered from acute haemorrhagic nephritis, i.e. have no known symptoms or signs of nephritis and in whom the routine urinalysis is completely negative, do not have subacute or latent nephritis. In the same year Snone (1937) published the results of a hundred and fifty-four cases which either he or Addis had followed for a period of ten years after the onset. All the cases had been examined at regular intervals clinically, and their urine by the Addis method. No case was considered to be healed unless the urine was consistently normal when examined by the Addis method for at least one year. Briefly his results showed that out of a hundred and three cases with an acute haemorrhagic onset, forty-four (42 per cent.) were healed, fifty-two (50 per cent.) were still active, and seven (6·8 per cent.) had died in advanced renal failure. He estimated that at least 33·3 per cent. would ultimately die of renal failure.

It is clear that the more stringent the criterion of cure, the worse is the prognosis. The contradiction between the results given by Boyle et al. and by Snone may be only apparent, since of sixteen cases in the present series which were actually in the latent stage, but in whom clinical and routine urine examination gave normal results, eleven or sixty-nine per cent. gave normal results on one or more occasions when examined by the Addis method. It is therefore possible that if repeated examinations of the urine had been made in the cases reported by Boyle et al., cases of latent nephritis would have been found although clinical and routine urinalysis and one examination by the Addis method gave normal results.

The results of the present series are in general agreement with those of Snone except that the percentage of healed cases is higher (sixty-four as compared with forty-two per cent.), the percentage of cases in the latent stage is lower (thirty-two as compared with fifty per cent.), and the estimated ultimate mortality, largely based on these figures, is lower (twenty-seven as compared with thirty-three per cent.). This discrepancy may be due to the criterion of cure in this series, which, although more strict than in those in which the urine was not examined by the Addis technique, was not as strict as in Snone's, repeated examinations over at least one year being impossible. With such repeated examinations some cases appearing normal on two occasions might have been found to be latent. That none of the cases died in advanced renal failure is probably due to the short interval between the initial attack and the period of review, and that no case was found to be in, or to have passed through, the active stage was probably fortuitous, as both Addis (1925) and Snone (1937) report cases which they have observed to pass into this stage after an acute haemorrhagic onset.

Effect on ultimate prognosis of various factors.

1. SEPTIC FOI, most commonly enlarged tonsils, were present in sixty-nine cases at the time of onset. Their removal before the child's discharge from the hospital had little, if any, effect on the ultimate prognosis, as shown by the following figures :

Septic foci were present at onset in sixty-nine cases. Now healed forty-four. Now latent twenty-five.

REMOVED WITHIN 3 MONTHS OF ONSET—41 cases. NOW HEALED 63·5 per cent.
REMOVED 3–12 MONTHS AFTER ONSET—10 cases. NOW HEALED. 50 per cent.

REMOVED 1–2 YEARS AFTER ONSET—3 cases. NOW HEALED. . . 100 per cent.
SEPTIC FOCUS STILL PRESENT—15 cases. NOW HEALED . . . 67 per cent.

This is difficult to correlate with the general impression and with the statement of Lytle and Rosenberg (1929) that the persistence or recurrence of infections is the most potent factor in producing chronic nephritis. Perhaps these figures are too small to be reliable. Or the removal of the apparent source of infection may not be enough to protect the individual from small subclinical infections. Kellett (1936) has shown that at the onset of acute haemorrhagic nephritis complement almost completely disappears from the blood, probably due to the premature production of antibody and a reversed anaphylactic reaction by which many, if not all, the cells of the body are injured. In spite of the removal

of the apparent source of infection, small infections of the skin or nasopharynx may occur, sufficient to upset the antigen-antibody balance, thus causing further renal damage. That this may often happen is shown by the case P.R. who was in hospital with acute haemorrhagic nephritis and reported ten months later. Her tonsils had been removed three weeks after the onset. Though she seemed perfectly well, examination of her urine by the Addis method showed haematuria. The mother was therefore instructed to keep her in bed and watch her carefully if she should have a cold or sore throat. Five months later the mother brought a small bottle of urine which was smoky and contained albumin, and stated that the child had had a sore throat two days previously, and had apparently completely recovered, but had passed this urine on her return from school that day. The private doctor examined the urine that evening and daily for a week and reported nothing abnormal. This undoubtedly, but mild, exacerbation following the sore throat, and in spite of tonsillectomy, would have been missed if the mother had not been watching for it. The removal of septic foci alone does not prevent exacerbations.

2. BED AND DIETARY TREATMENT.—The cases have been grouped according to the duration of bed treatment and dietary restriction during the acute attack. Results were as follows :

IN BED LESS THAN 6 WEEKS—21 cases.	HEALED	67 per cent.
IN BED 6-12 WEEKS—27 cases.	HEALED	74 per cent.
IN BED 12 WEEKS OR MORE—29 cases.	HEALED	65·5 per cent.
LOW PROTEIN DIET LESS THAN 6 WEEKS—21 cases.	HEALED	75 per cent.
LOW PROTEIN DIET 6-12 WEEKS—23 cases.	HEALED	65 per cent.
LOW PROTEIN DIET 12 WEEKS OR MORE—39 cases.	HEALED	61·5 per cent.

The length of bed treatment and dietary restriction are usually proportional to the severity of the attack, but do not seem to have any significant effect on the ultimate prognosis. When the cases are grouped according to the severity of the initial attack the same result is shown.

3. TYPE OF INITIAL ATTACK

ACUTE FOCAL—21 cases.	HEALED	67 per cent.
ACUTE DIFFUSE. MILD—27 cases.	HEALED	74 per cent.
ACUTE DIFFUSE. MODERATE—28 cases.	HEALED	64·5 per cent.
ACUTE DIFFUSE. SEVERE—7 cases.	HEALED	57 per cent.

In view of the small number of cases which had severe initial attacks, the fall in the percentage of cured cases is probably not significant. These conclusions are in agreement with those of Lytle and Rosenberg (1929) and of Snone (1937), all of whom concluded that the liability of the disease to become chronic is not proportional to the severity of the initial attack.

2. Cases with subacute, or acute tubular onset.—Fourteen children have been admitted to hospital in the last four years in the active or subacute stage of nephritis with no history of acute glomerular nephritis. Six of them have died in the active stage with or without a superimposed infection, and one died at home five and a half years after the onset. The actual mortality has thus been fifty per cent. Of the remaining seven, none are normal. Five are latent and apparently in good health, but with excess of either red blood corpuscles or protein in the urine. Two of these have had pneumococcal peritonitis

since the onset of the nephritis. Four of them having had nephritis for more than two years are unlikely to recover. The remaining two are still in the active stage. The ultimate mortality will be seventy-nine per cent. even if these two patients and the two who have been latent for less than two years after the apparent onset recover.

These results again give a worse prognosis than those of Lytle and Rosenberg (1929) in whom the urine was not examined by the Addis method. They reported that of twenty-five cases of acute glomerulo-tubular or acute tubular nephritis, the immediate mortality was twenty-eight per cent. and another twenty per cent. became chronic, the remaining fifty-two per cent. being apparently normal. The results of the present series are in fairly close agreement with those of Snone (1937) who found that of fourteen cases first seen in the degenerative stage with no history of acute haemorrhagic nephritis, one had recovered, one was in the latent stage, two were still in the degenerative stage and six (forty-two per cent.) were dead of renal failure.

That children can remain in apparently good health for many years after the active stage and yet ultimately pass into the terminal stage is shown by a case O.K., not included in the above figures, because she was first admitted before the period of this review.

She was in this hospital eight years ago with subacute nephritis. After several months she apparently recovered and attended school for eight years. She then had an attack of cramps in her hands and feet and was examined by a doctor who found albuminuria. A few months later she was readmitted and found to be in the terminal stage with nitrogen and phosphorus retention.

The ultimate prognosis in this type of nephritis is grave. The probable explanation is that these children have already had unnoticed acute glomerular nephritis, so that although the onset of the nephritis appears to be with the onset of the oedema, actually they have had nephritis for some time previously and their kidneys are already seriously damaged when they are first seen.

This was suggested by Parsons (1926); since then the evidence has grown much stronger. Lytle (1933) reported fourteen cases of scarlet fever without symptoms or signs of nephritis, who all showed excess of protein, cells and casts in the urine by Addis counts between the eighth and forty-eighth day of the disease. Gram (1936) found that of eight cases of scarlet fever without manifest nephritis, all excreted excess of red blood cells and casts in the urine at some time during the disease, and concluded that the majority of cases with scarlet fever have latent or, as Snone would term it, 'micro'-nephritis. Goldring (1931) showed that thirty-eight out of forty-four previously healthy patients with acute lobar pneumonia excreted excess of albumin or formed elements in the urine during the acute stage of the disease. Albuminuria, cylindruria and excess of white and epithelial cells occurred so commonly that he concluded that they indicated only minimal renal damage, but haematuria occurred in sixteen cases and was thought to indicate more serious renal damage.

Thus evidence accumulates of kidney injury in most acute infections, and although the majority are left without serious renal damage, the high mortality in those children who are first seen with subacute or acute tubular nephritis may be due to serious renal damage acquired during a previous infection, or perhaps a series of subclinical attacks. There is a tendency to refer to these

cases as mixed types when they apparently start as pure nephrosis and are later found to have haematuria. I think that they are actually cases of nephritis from the onset, and that their prognosis is that of subacute nephritis.

As Snode (1937) pointed out, it may be extremely difficult to demonstrate haematuria in the presence of heavy albuminuria. It is generally agreed that cases of nephrosis do not develop renal failure, and there seems to be no reason why they should develop a superimposed nephritis. As Kellett showed, the development of nephritis is probably due to a certain state of resistance of the body to an infection, and is not a local condition apt to develop in previously damaged kidneys.

3. Cases with insidious onset.—Ten children in whom the onset of nephritis was insidious have been followed. The presenting symptom in five cases was malaise, or loss of appetite, in two it was puffiness of the face, and in three there were no symptoms, but albuminuria was discovered in routine examination of the urine during an acute infection (measles, two cases ; scarlet fever, one case). In most cases there was no known preceding infection ; in three cases the albuminuria followed or accompanied scarlet fever, and in two cases measles. In none was there gross haematuria or oedema. In a few there was slight nitrogen retention at the time of the discovery of the renal lesion. Of these ten cases, four are now healed. Of the remaining six, one has been in the active or subacute stage for more than two years, three are in the terminal stage with hypertension, and the remaining three have had the renal disease for three to five years, being still in the latent stage and are unlikely to recover. These results are similar to those of Snode (1937) who found that of eleven such cases, five had recovered and of the remaining six, one had died and four were unlikely to recover. Such cases, in which the ultimate prognosis is graver than the mild and unimpressive symptoms at the onset indicates, seem to pass into the terminal stage almost unnoticed. These probably include two types : (1) cases which after a mild unnoticed initial attack are already when first examined in the convalescent stage and may recover spontaneously, and (2) cases which, having passed through the initial attack and latent stage unnoticed, are in or approaching the terminal stage when first examined. That they may pass through all the preliminary stages unnoticed is well recognized. Only one such case was found in the present investigation, and she died in the terminal stage three months after the onset of symptoms.

Anaemia

References in the literature to anaemia in nephritis are few. With a view to determining the incidence and degree of anaemia in each stage of nephritis, blood examination was made in as many cases as possible in the present series, and on cases of acute nephritis in the wards during the past nine months. These have been supplemented by any blood counts which have been available on the cases during their previous admissions.

In the acute stage of haemorrhagic nephritis, during the first three weeks of the disease half the blood counts gave a haemoglobin reading below eighty per cent. In the second three weeks twenty-five per cent. of the counts gave haemo-

globin values below eighty per cent, and the haemoglobin at a later stage was almost invariably about eighty per cent. (fig. 1). Severe anaemia in the acute stage was unusual except in the presence of sepsis or immediately after tonsillectomy. The rise of haemoglobin in the majority without iron medication, although the diet was still restricted, suggests that the slight anaemia in the first three weeks was due to the infection associated with the nephritis rather than to blood loss, a suggestion in keeping with the fact that the colour index was rarely below normal in the first three weeks. In three cases out of seven in which iron was not given and no complication was present, the haemoglobin remained below normal or actually fell after the toxæmia had passed off, the colour index being lower at the end of the period of observations than at the beginning (average 0.86 to average 0.78). This together with the rise in haemoglobin in those patients anaemic in the early stages, who received iron

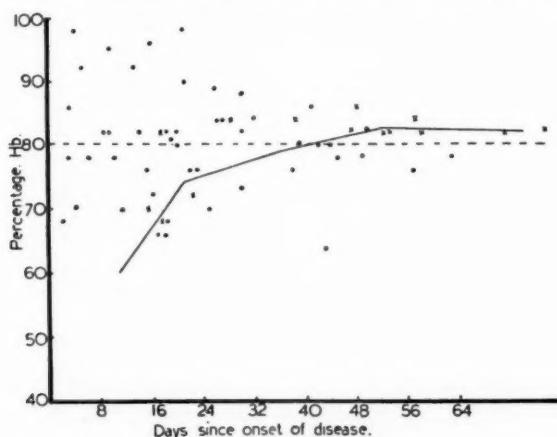


FIG. 1.—Chart showing haemoglobin of cases of acute nephritis plotted against the day of the disease. Cases with obvious sepsis or recent tonsillectomy have been excluded.

Dots indicate that no iron was being given at the time of the blood examination. X indicates that iron was being given at the time of the blood examination. Solid line is the mean between the crosses and indicates mean course of the cases receiving iron.

medication, suggests that in some cases the loss of blood by the kidneys and the restricted diet is sufficient to cause a mild deficiency anaemia. Mild anaemia (haemoglobin sixty-six to seventy-eight per cent.) was present in all five patients who were examined within a week of tonsillectomy, but recovery was rapid in all except one, in whom a septic focus persisted. In the child in whom sepsis was present at the time of the first examination, anaemia was severe (haemoglobin fifty per cent.).

These results are at variance with those of Gladys Boyd (1937) who stated that secondary anaemia is a constant complication of acute nephritis and is proportional to the blood lost by the kidneys. She found that a diet high in vitamin E, including milk, fruit and vegetables as early as possible after the onset appeared to prevent severe anaemia.

It is difficult to reconcile these apparently contradictory findings except by the suggestion that the cases to which she referred were more severe than most of the cases in this series.

The blood counts of twenty-nine patients completely recovered from acute nephritis, and thirty-six patients still in the latent stage without nitrogen retention or hypertension (table 1) show no evidence of anaemia in the latent stage of nephritis. There was no deviation from normal in those children in whom the nephritis having been latent for more than two years was unlikely to recover completely.

TABLE 1

	HEALED		LATENT	
	RANGE	AVERAGE	RANGE	AVERAGE
Haemoglobin, per cent.	76-98	87	80-104	89
Red blood cells, millions per c.mm.	4.5-5.58	5.12	4.5-6.2	5.33
Colour index	0.77-0.97	0.85	0.75-1.05	0.84
Haematocrit, per cent.	32.1-42.1	37	35-47	38.2
Mean corpuscular volume	64.8-81.5 μ^3	72 μ^3	62.5-81 μ^3	72 μ^3

Blood counts in five cases in the subacute or active stage with oedema, but no nitrogen retention or sepsis results were as follows :

	RANGE	AVERAGE
Haemoglobin, per cent.	90-96	91
Red blood cells, millions per c.mm.	4.16-5.96	5.33
Colour index	0.76-0.91	0.85
Mean corpuscular volume	65.8-73 μ^3	69.5 μ^3

A Price-Jones curve in a typical case was normal (fig. 2). One child was observed in the active stage of nephritis with oedema and no sepsis and was found to have haemoglobin ninety-eight per cent. and red blood cells 5.8 million per c.mm. About one month later she was readmitted with pneumococcal septicaemia which caused her death twelve days later. On readmission her haemoglobin had fallen to eighty per cent. and it fell rapidly to seventy per cent. before death. These results suggest that anaemia is apparent rather than real in the majority of cases with uncomplicated subacute nephritis, but develops in the presence of sepsis.

Only six children have been examined in the terminal stage of chronic nephritis with either hypertension or nitrogen retention, but blood counts are available for other children with renal failure and renal rickets (table 2). None of the children had obvious sepsis at the time of the blood count, and all had apparently had renal failure for several months or years (table 2).

Anaemia was present in five out of nine cases, severe in three. With one exception it was orthochromic and normocytic. A Price-Jones curve in a typical case was normal (fig. 3). The reticulocyte count was consistently low and the van den Bergh reaction negative. Anaemia was present in only one case (O.K.) with blood urea under 100 mgm. per cent. and was present in all except one of those with blood urea above 100 mgm. per cent., but its severity was not proportional to the degree of nitrogen retention (fig. 4). Neither was the severity

TABLE 2

CASE	HAEMOGLOBIN PER CENT.	RED BLOOD CELLS, MILL. PER C.MM.	COLOUR INDEX	HAEMATOCRIT PER CENT.	MEAN CORPUSCULAR VOLUME	BLOOD UREA MGM. PER CENT.	CA. MGM. PER CENT.	P. MGM. PER CENT.	BLOOD PRESSURE MM. HG.
J.Fen...	110	6.77	0.81	48	$71\mu^3$	26.7 (N.P.N.)	—	—	154/100
B.H. .	104	5.63	0.92	41.2	$73\mu^3$	44	—	—	120/80
W.J. .	100	5.41	0.92	42	$77.5\mu^3$	37.5 (N.P.N.)	—	—	156/120
J.F. .	84	5.20	0.81	34	$65.4\mu^3$	50	—	—	190/150
J.D. .	80	4.46	0.90	—	—	239	5.8	13.0	—
N.Y. .	74	4.58	0.81	33	$72\mu^3$	105	—	—	160/110
D.N. .	74	4.12	0.90	29	$70.5\mu^3$	195	8.1	6.82	104/74
O.K. .	60	3.80	0.79	26	$68.5\mu^3$	70	8.4	9.04	124/84
C.H. .	52	3.23	0.81	25	$77.5\mu^3$	179	10.1	5.7	128/110
D.H. .	52	3.48	0.74	—	—	148	8.95	6.67	100/70

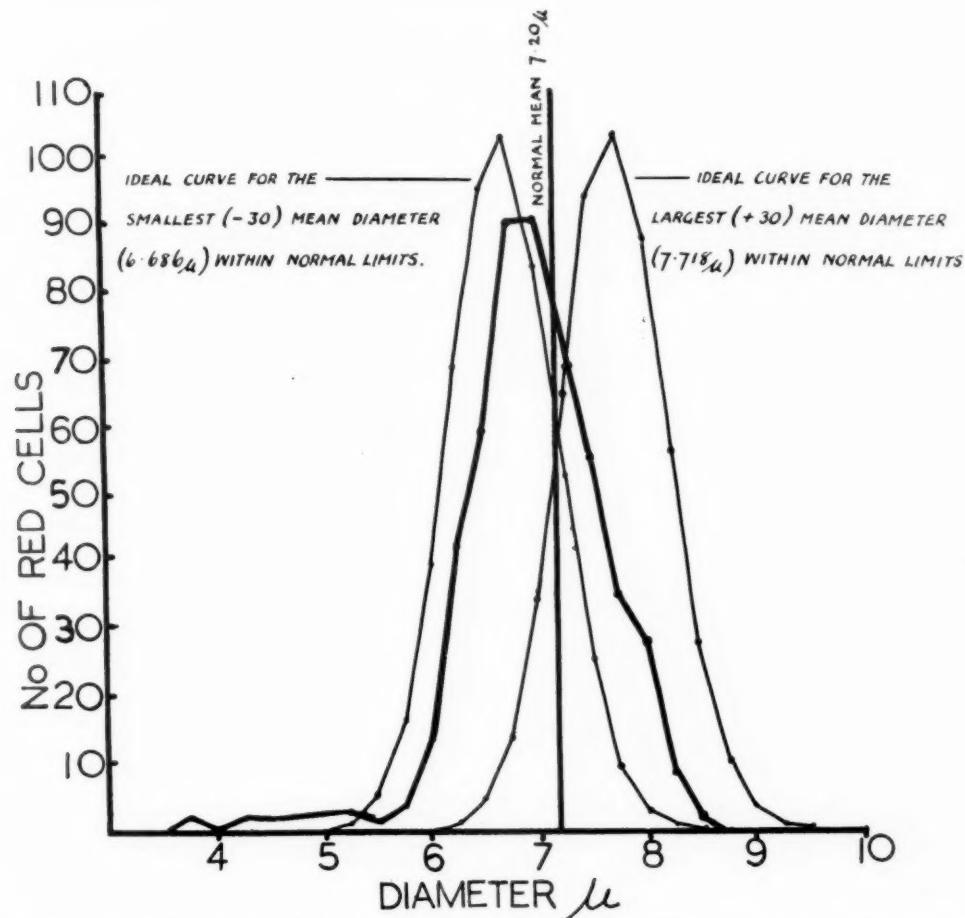


FIG. 2.—Price-Jones curve in case of active or subacute nephritis. RBC 5.5 mill./c.mm. Hb 90 per cent. C.I. 0.82. Mean corp. vol. 69.4μ . Mean diameter $7.0\mu \pm 0.59\mu$. V 8.4 per cent. Microcytosis 0.8 per cent.

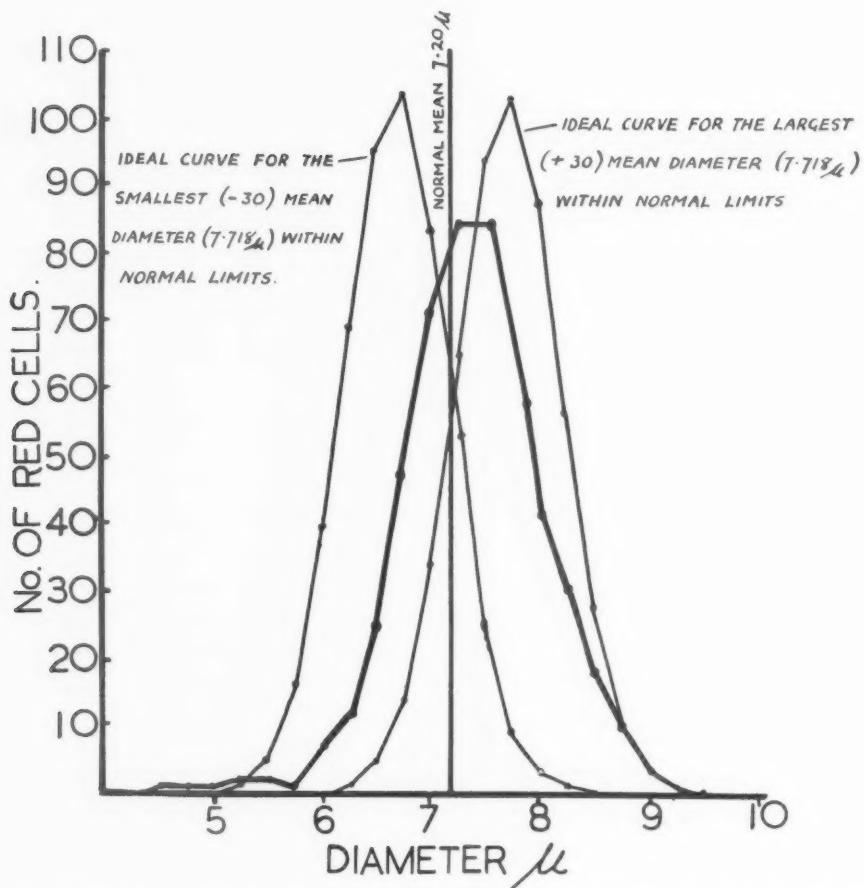


FIG. 3.—Price-Jones curve in case (C.H.) of chronic renal failure. RBC 3.23 mill./c mm.
Hb 25 per cent. C.I. 0.81. Mean corp. vol. $77.5\mu^3$. Mean diameter $7.37\mu \pm 0.66\mu$.
V 8.4 per cent. Microcytosis 0.8 per cent.

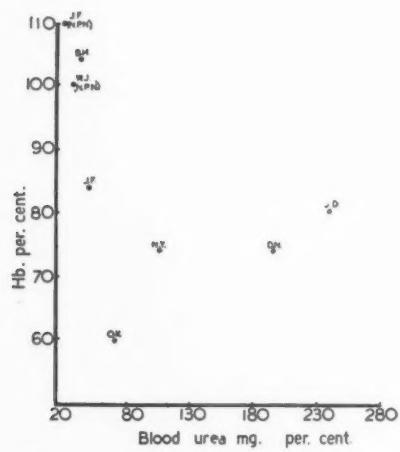


FIG. 4.—Chart showing haemoglobin of cases of chronic nephritis and renal rickets plotted against blood urea or NPN—see table.

of the anaemia proportional to the degree of hypertension, the depression of the serum calcium or the elevation of the serum phosphorus. Anaemia did not occur with depression of the serum proteins in the cases of nephritis in the active stage of the disease.

These findings do not support the statement of Osgood et al. (1932) that anaemia is so constant in chronic nephritis that it is useful in the differential diagnosis of this condition from hypertensive renal disease in which anaemia rarely occurs. On the other hand, when Mitchell (1930) in reviewing cases of chronic interstitial nephritis, especially when complicated by renal rickets, stated that in practically every instance in which the blood was examined, secondary anaemia was found, he was probably dealing only with severe and late cases similar to those with renal rickets and anaemia in the present series.

The chart (fig. 5), showing the principal findings in a case of chronic nephritis over a period of four and a half months, demonstrates several of the many factors which complicate the study of anaemia in this condition.

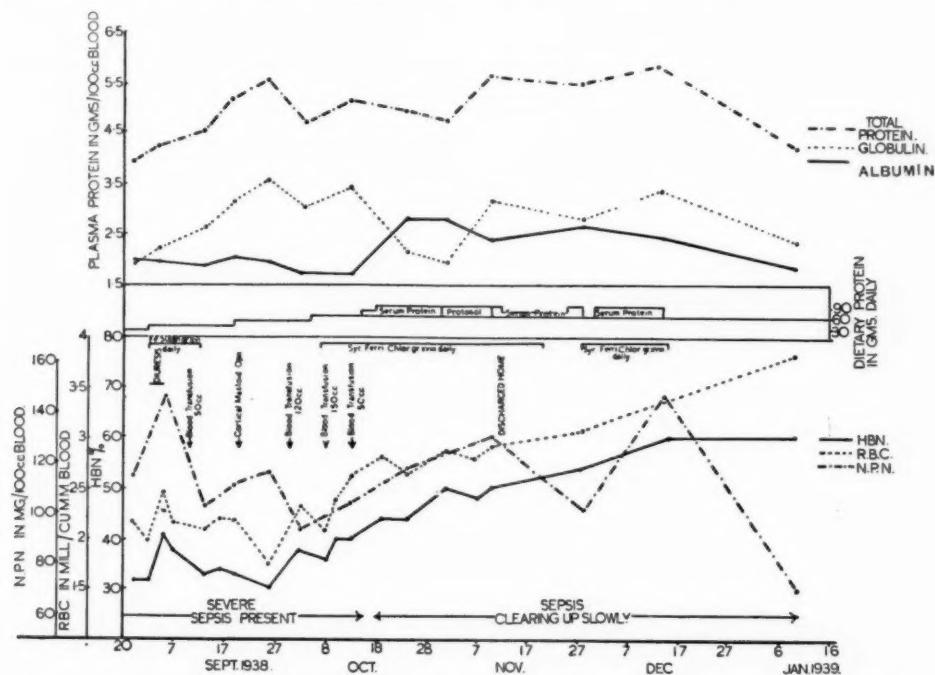


FIG. 5.—Chart showing main findings on blood examination in the case O.K., 14 years of age, over a period of 4½ months—see text.

The child is the one (O.K.) previously referred to, who was known to have had subacute nephritis eight years previously, but who had remained in apparent good health and attended school until three months before admission. She then had an attack of tetany and remained at home on a meat-free diet. For two weeks before admission she had a painful swelling behind the right ear. On admission she was pale, slightly puffy, undersized and with no signs of puberty, and had acute mastoiditis. The chief blood findings are shown on the chart. Her serum calcium was 5.9 mgm. per cent., serum phosphorus 10.4 mgm. per cent., and phosphatase 2.4 units. Her urine was dilute and contained red blood corpuscles and 13.8 gm. of protein daily. The albuminuria fell to an

average of 7 gm. daily during the last month in hospital. Three days after admission she had a diuresis of sixty-three ounces daily for three days. At the end of that time her haemoglobin and non-protein nitrogen had risen slightly, but they both fell rapidly to their previous level. A small blood transfusion had no effect on the anaemia. A mastoid operation was performed three weeks after admission and was followed by a slight temporary fall in the haemoglobin and red blood cell count, and rise in the blood non-protein nitrogen. For the next three weeks the mastoid wound was unhealthy with offensive sloughs and much discharge. The child was given three blood transfusions, each of which was followed by a slight rise in the haemoglobin, but in spite of the transfusions the plasma albumin tended to fall and the wound remained unhealthy. By this time her dietary protein had been raised to sixty grammes daily (1 gm. per pound body weight), and she was taking a diet high in vitamin C with added vitamin B. She was then given an additional thirty grammes of protein daily in the form of serum protein prepared in the biochemical laboratory under the direction of Dr. Hickmans. This was followed by an immediate improvement in her general condition and in the mastoid wound, and in a rise of plasma albumin and fall in plasma globulin, the total protein remaining practically stationary. At the same time the blood non-protein nitrogen and haemoglobin began to rise. After ten days of this treatment, an equivalent amount of protosol was substituted for the serum protein. The plasma albumin fell slightly, but the total plasma proteins rose because of a rise in the globulin, the non-protein nitrogen continued to rise, the haemoglobin remained stationary, and it was the opinion of the ward sister and of the house physician that the child did not seem quite so well. She was therefore given the serum protein again, but she was discharged home three days later and took only about fifteen grammes daily for a fortnight. When next seen, her general condition was about the same, the mastoid wound was granulating, but still discharging a little thin sero-pus, the anaemia was improving slowly, and the blood non-protein nitrogen had fallen to below 100 mgm. per cent. The plasma albumin had risen slightly but was still lower than the globulin, and the total plasma proteins were unchanged. She was then given serum protein thirty grammes daily for two weeks. At the end of this time the mastoid wound was about the same, and she complained of anorexia. It was found that the non-protein nitrogen had risen to 146 mgm. per cent. The plasma albumin had fallen slightly, but the total plasma proteins had risen to 5.8 gm. per cent. and the haemoglobin to sixty per cent. In view of the anorexia and rise in non-protein nitrogen, the extra protein was discontinued, and she was given a liberal diet including meat with about sixty grammes of protein daily. After three weeks on this diet her appetite had improved and she felt better, the non-protein nitrogen had fallen to sixty-nine mgm. per cent. the haemoglobin was stationary at sixty per cent., but the red blood cells had risen to 3.8 millions per c.mm. The plasma proteins had fallen to their original low level, and the mastoid wound was still about the same.

The following are the chief points which emerge from this case :

(1) The severity of the anaemia was not proportional to the depression of the plasma proteins or the elevation of the non-protein nitrogen, but it was most severe at the time of severe sepsis and gradually improved as the sepsis cleared up. It is not suggested that sepsis is the only cause of the anaemia in such cases, but it clearly aggravated the anaemia in this case. It was unfortunately not possible to follow the case further, but the rise in the red blood cell count during the last three weeks, which coincided with a marked fall in the

nitrogen retention, suggests that the high non-protein nitrogen also had had a depressing effect on the bone marrow. In view of the renal failure this child is unlikely ever to be free from anaemia, even in the complete absence of sepsis. The administration of iron had no apparent effect on the course of the anaemia.

(2) The first administration of serum protein was accompanied by a marked and rapid rise in plasma albumin and improvement in general condition ; its continued administration only maintained the same level of plasma albumin, but caused a gradual rise in total plasma proteins, a good effect counterbalanced by a rise in non-protein nitrogen. In such a case, unusual in its combination of gross albuminuria with severe nitrogen retention, sufficient serum protein to replenish plasma proteins can probably not be administered without increasing the nitrogen retention. The quick initial response of the plasma proteins to feeding with serum proteins, followed by the later gradual response, resembles the findings by Weech and Goetsch (1938) in dogs to whom they fed serum protein after prolonged depletion of plasma proteins, and may be due, as they suggest, to the slow recovery of the organ—probably the liver—which is responsible for the regeneration of plasma albumin. The less marked improvement in general condition when the equivalent amount of protein was administered as protosol, and the return to the abnormal albumin : globulin ratio, appear in the light of later developments to have been fortuitous only, or due to the increasing nitrogen retention.

Summary

Prognosis.—A hundred and twenty cases of nephritis which had been in the Children's Hospital, Birmingham, were examined, and were grouped into healed, latent, active, or terminal cases according to the urinary findings and blood chemistry. Those in the latent stage were usually free from symptoms with normal blood chemistry, but a few exceptions were noted. There was no change in the plasma proteins which could be considered typical of any one stage of the disease, but they were abnormal in all the cases in the active or subacute stage.

Eighty-eight cases of acute haemorrhagic nephritis who were first admitted in the initial attack, have been examined six months to five years after the onset. The mortality in the acute attack was 3·4 per cent. Two cases were found to be in the terminal stage with hypertension. Thirty-two per cent. of the cases were in the latent stage, and sixty-four per cent. were healed. The estimated ultimate mortality was twenty-seven per cent.

The liability of the disease to become chronic was not affected by the removal of the apparent focus of infection, usually infected tonsils, in the acute stage of the disease nor was it related to the severity of the initial attack, nor to the length of bed or dietary treatment in the initial attack.

Fourteen cases who were first seen in the active or subacute stage of nephritis were examined. The actual mortality was fifty per cent. and the probable ultimate mortality was at least seventy-nine per cent.

Ten cases of nephritis with insidious onset have been examined. Four have recovered and the remaining six are unlikely to recover.

Anaemia.—Cases in the initial acute attack, healed, latent, active and terminal stages have been investigated for anaemia.

In the acute initial attack the anaemia was slight, tended to recover spontaneously, and was probably due to the infection associated with nephritis. In a few cases there was evidence of mild hypochromic anaemia, probably due to a combination of haematuria and restricted diet.

No anaemia was found in the latent stage of nephritis.

No anaemia was found in the subacute or active stage of nephritis except in the presence of sepsis.

In the terminal stage, anaemia was found to be a late complication and was nearly always accompanied by marked nitrogen retention. It was orthochromic and normocytic with no evidence of haemolysis. One case is discussed in detail.

It is a pleasure to express thanks to the following :

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ABSORPTION STUDIES IN CHILDREN WITH GIARDIA LAMBLIA INFECTION

A Preliminary Report

BY

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Infection of children with the flagellate giardia lamblia often causes abdominal symptoms, anaemia and defective development. It is not known how these symptoms originate. Abdominal pains are most probably connected with the mechanical action of the protozoa. Anaemia may be due to the fact that the parasites inhabit and thus damage a part of the body which plays an important part in haematopoiesis. No satisfactory explanation has been offered for the interference with development, since the small amount of foodstuffs withdrawn by the parasites cannot be sufficiently great to cause severe loss. This circumstance led me to examine the conditions of absorption in children infected with giardia lamblia.

Particular attention was paid to fat absorption. Cursory examinations had already revealed abnormalities in this function, and Miller (1926) had observed that typical steatorrhea was a common condition in the giardia epidemics in the Great War. Concentration of urinary pigments was also estimated. The value of this latter is not always characteristic of intestinal absorption, neither are the changes proportional. But if absorption in the bowel is hindered by some cause a high proportion of the biliary pigments will be excreted in the faeces and the amount of pigments in the urine thus lessened.

The determinations were made in seventeen children selected from one hundred and eighty-eight giardia-infected patients. Their ages varied from two to fourteen years. The following data are twenty-four-hour averages of experiments lasting forty-eight or seventy-two hours. Fat determinations were made by the method of F. Müller (1887) and the estimation of urinary pigments by that of Veil (1927) and Heilmeyer (1927).

Absorption of fat

About 90 to 97 per cent. of the fatty substances taken by mouth are absorbed in a healthy organism under normal conditions when a normal diet is given ;

the fat excreted amounts to about 10 to 15 per cent. of dried faeces. Fat absorption was examined in fourteen children. The data of importance are given in table 1. Similar cases were put in one group ; the values given are averages from the single instances.

TABLE 1
INTAKE AND EXCRETION OF FAT

NUMBER OF CASE	FAT INTAKE IN GM.	FAT EXCRETED IN FAECES		FATTY ACIDS IN PERCENTAGE OF EXCRETED FAT		<i>pH</i>
		IN PER-CENTAGE OF FAT INTAKE	IN PER-CENTAGE OF DRY SUBSTANCE	FREE	SAPONIFIED	
3, 7, 9, 12 ..	48.05	4.41	9.07	20.0	45.5	6.9
4, 10, 13 ..	49.04	24.83	35.47	47.0	29.2	5.0
5, 11, 17 ..	82.30	47.57	41.53	41.0	37.6	4.6
1, 2, 15, 16 ..	40.44	77.68	51.83	58.9	15.9	3.8
1, 2, 15, 16 ..	12.53	79.20	26.87	62.2	12.2	3.8

As can be seen, only the four children of the first group show normal absorption, while those of the second, third and fourth groups all reveal abnormal absorption. Members of the fourth group do not retain more than a fifth of the consumed fat and more than the half of the dry substance of their faeces consists of fat, but not as if the fat content of the food were excessive. The patients of the fourth group were examined after reducing the fat in their original diet to a third. The last line of table 1 shows the results. It is clear that the absorptive capacity has not improved after the reduction of fats, the only difference being that a smaller part of the dry substance is formed of fats. After such a dietetic measure the condition of the patients, if judged by the appearance of their stools, seems to be improved, although the absorptive capacity is invariably imperfect.

Interference with absorption of such severity is usually due to pancreatic inactivity. This cause could be excluded in the present cases by determining the fermentative processes. Determination of the lipolytic activity of the faeces was made in every instance, with the stalagmometric method of Rona and Michaelis (1911). The values resulting were over 90 per cent. in nine cases, between 80 and 90 per cent. in two, and between 75 and 80 per cent. in three patients. The lowest value obtained, 76 per cent., must still be regarded as normal. Thus the impaired absorptive capacity is not the consequence of a lack in some ferment. Analyses of the excreted fat demonstrate this too. (See the fifth and sixth columns of table 1.) Apart from the first group, the proportion of free fatty acids exceeds that of the saponified ones. In other words the consumed fat, though split in the intestine, cannot be absorbed. The excessive amount of free fatty acids leads to the acidifying of the intestinal contents. (See the *pH* values in the last column of table 1.) This circumstance, together

with the fact that the absorption of other materials and of water is similarly impaired, explains the continuous diarrhoea of these patients and the unusually large quantity of stools passed.

The fats are, accordingly, digested but not absorbed. Only two conditions can cause this if the fermentative activities are normal. One is the lack of the adrenocortical hormone regulating the synthesis of fats. Such a condition would, apart from the abnormality of absorption, show itself by several other symptoms, none of which was detectable in the patients in question. Thus it has to be assumed that there is a mechanical obstacle to absorption, in the present cases the impermeable layer of parasites covering the surface of the bowels.

Urinary pigments

According to Veil and Heilmeyer the concentration of pigments in the urine of normal individuals is about $F_0 = 1.80$, and the total amount of pigments excreted during twenty-four hours, $F \times M$ = between 9.0 and 11.0. In healthy children the F_0 value is commonly over 1.0, and the value of $F \times M$ between 8.0 and 9.0. Determinations were made in thirteen out of the seventeen children. Two of them, having affections of the liver demonstrable also by other means, gave pathologically high values, while normal ones were found in three children. The values of all the remaining eight patients were much below the normal. Two showed F_0 values under 0.1 and $F \times M$ under 1.1; in four others the F_0 was found between 0.1 and 0.2, $F \times M$ between 1.20 and 2.10.

No condition has been known up to now in which the amount of urinary pigments would be lessened. F_0 values may be low in polyuria, but no such symptom could be seen in these patients, and the $F \times M$ values show that not only the concentration of the pigments has decreased but their absolute amount is reduced also. There is only one explanation of this circumstance: the intestinal wall has, owing to some cause or other, become impermeable so that not even the readily absorbable bile can be absorbed.

Treated cases

The above-mentioned experiments have shown that absorption is hindered in these patients and that the hindrance is of a mechanical character. It has been assumed that the obstacle is a layer of parasites adhering to the wall of the intestine. If this assumption is correct, after the expulsion of the protozoa the absorptive capacity should become normal again.

Eight of the seventeen children were treated with arsenic and acridine compounds. No other medicines were given and no dietetic measures taken. The parasites disappeared in every instance, the longest duration being seven weeks. The abnormality of absorption began to improve at once in every case when treatment was started and conditions became perfectly normal in ten to twelve weeks. Table 2 shows the values before and after treatment of the three severest cases which figured in the fourth group of the first table.

TABLE 2

FAT ABSORPTION AND URINARY PIGMENT VALUES BEFORE
AND AFTER TREATMENT

NUMBER OF CASE	TREATMENT	FAT EXCRETED IN FAECES		URINARY PIGMENT	
		IN PERCENTAGE OF FAT INTAKE	IN PERCENTAGE OF DRY SUBSTANCE	F ₀	F × M
2	Before	77.90	58.0	0.095	0.99
2	After	5.60	7.7	1.79	8.0
15	Before	77.40	42.0	0.09	0.82
15	After	5.20	12.1	1.93	8.75
16	Before	73.60	60.5	0.17	1.52
16	After	7.10	9.3	1.44	9.32

It can be seen that the absorption of fats became normal after treatment. The fat in the faeces does not amount to more than one-tenth of the dry substance. The concentration and total amount of pigments in the urine show normal values. Anaemia and the great retardation of development have also shown a parallel improvement.

These experiments prove the pathogenicity of *giardia lamblia*, which is still doubted by some authors, and partly explain the mode of origin of the symptoms caused by the flagellate. Apart from the lesion of organs playing a part in haematopoiesis, the impaired absorption may have a rôle in the origin of anaemia, and it is this which possibly causes the retardation of development so often seen in *giardia*-infected children.

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THE BLOOD AND SPINAL FLUID SUGAR AND CHLORIDE CONTENT IN MENINGITIS

BY

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It has long been recognized that the cerebrospinal fluid contains glucose and chlorides and that in meningitis their amount is reduced. This is generally supposed to be of diagnostic importance in distinguishing meningitis from certain other diseases in which there is a meningeal reaction, such as acute anterior poliomyelitis. In the present paper a study of the sugar and chloride content of the cerebrospinal fluid from children suffering from conditions other than meningitis (control series) and from cases of meningitis has been made, and the results correlated with the sugar and chloride content of the blood. The control series consisted of seventeen cases with no organic meningeal disease and from whom lumbar puncture, performed for diagnostic purposes, yielded a normal cerebrospinal fluid. Care was taken to exclude all cases in which there had been convulsions, as these have been proved to cause a marked alteration in the blood sugar content (MacLean, 1936). Of the meningitis cases there were twenty-eight with tuberculous meningitis, fourteen with meningococcal, one with pneumococcal, two with *B. coli*, two with influenzal and one with benign lymphocytic meningitis. All the cases had fasted for at least five hours before the blood and cerebrospinal fluid were taken. The blood was always obtained immediately before the lumbar puncture was performed as withdrawal of cerebrospinal fluid is known to cause a substantial rise in the blood sugar (Weichsel and Herzger, 1936).

Methods.—The blood and spinal fluid sugar was estimated by the modified Folin-Wu (1920) method on 0·2 c.c. of blood and 1 c.c. of cerebrospinal fluid. For chloride estimations, 1 c.c. of blood or cerebrospinal fluid was used under the conditions worked out by Whitehorn for performing the Volhard titration method (Van Slyke, 1924).

The percentage of sugar in the cerebrospinal fluid

Normal fluid.—From a review of the literature it appears that in normal subjects there are wide variations in the percentage of sugar in the cerebrospinal fluid. The findings obtained by various writers (table 1) show a wide range of normality, but the lowest finding is not less than 35 mgm. per cent. The results obtained in the present investigation are similar though the lowest

limit is here 50 mgm. per cent. (table 2). Possibly the wide variations may be explained by concomitant variations in the blood sugar content. It is known that, even in normal circumstances, the blood sugar is subject to wide fluctuations; thus excitement, pain or the ingestion of carbohydrate produce striking alterations and it seems reasonable to suppose that the cerebrospinal fluid sugar will show similar changes. If this is in fact the case, then, in spite of variations in the blood sugar content, the ratio of cerebrospinal fluid sugar to blood sugar should be constant. Table 3 gives the results arrived at by various workers. This shows a wide range and reference to table 2 shows an equally wide range in the cases investigated. The lowest ratio found by other workers is 0·42 while in the present series it is 0·60.

TABLE 1
THE CEREBROSPINAL FLUID SUGAR CONTENT IN NORMAL CASES

OBSERVER	C.S.F. SUGAR IN MGM. PER CENT.	
	MAXIMUM	MINIMUM
Wright, Herr and Paul (1931)	80	45
Cohn, Levinson and McCarthy (1933)	75	38
Nissen (1937)	65	35
Rimle (1938)	60	40
Goodwin and Shelley (1925)	77	40
Hendry (present series)	83	50

TABLE 2
BLOOD AND CEREBROSPINAL FLUID SUGAR CONTENT IN CASES
NOT SUFFERING FROM MENINGITIS (CONTROL SERIES)

CASE	BLOOD SUGAR MGM. PER CENT.	C.S.F. SUGAR MGM. PER CENT.	RATIO OF C.S.F. TO BLOOD SUGAR	DIAGNOSIS
1	80	67	0·83	Diabetes mellitus
2	71	56	0·78	Microcephaly
3	81	65	0·80	Pneumonia
4	100	71	0·71	Mental deficiency
5	71	61	0·86	Hysteria
6	80	60	0·75	Malnutrition
7	104	83	0·87	Mental deficiency
8	82	66	0·81	Pneumonia
9	81	69	0·85	Nephritis
10	100	76	0·76	Mental deficiency
11	92	71	0·78	Spastic diplegia
12	68	50	0·72	Tonsillitis
13	95	61	0·64	Spastic diplegia
14	79	51	0·64	Congenital lues
15	90	60	0·66	Hydrocephalus
16	95	80	0·84	Gastro-enteritis
17	76	50	0·60	Mental deficiency
Average		64	0·76	

There is a possible explanation of this apparent lack of correlation between the blood and cerebrospinal fluid sugar content. If changes in the blood sugar content are not immediately reflected in the cerebrospinal fluid sugar content,

TABLE 3

THE RATIO OF CEREBROSPINAL FLUID SUGAR TO BLOOD SUGAR
IN NORMAL CASES

OBSERVER	RATIO OF C.S.F. TO BLOOD SUGAR				
	MAXIMUM			MINIMUM	
Wilcox and Lytle (1923)	0.70	0.50
Levinson (1925)	0.75	0.50
Greenfield (1930)	0.65	0.45
Cohen (1936)	0.93	0.52
Stewart (1928)	0.82	0.42
Hendry (present series)	0.87	0.60

in other words if there is a lag in the transference of sugar from the blood to the cerebrospinal fluid, then, in the event of there being a sudden change in the blood sugar percentage, any correlation that may exist will not show itself until some time after this change takes place. To test this hypothesis an opportunity occurred to raise the blood sugar level rapidly by giving intravenous glucose and subsequently to examine the spinal fluid and the blood. It is known that when glucose is given intravenously there is a sudden rise in the blood sugar content up to about 300 mgm. per cent., followed by a rapid fall so that at the end of about one hour it has returned to approximately the normal level (Crawford, 1938). In table 4 the results of this experiment are shown. From this it will be seen that the ratio of fasting cerebrospinal

TABLE 4

BLOOD AND SPINAL FLUID SUGAR CONTENT AND RATIO OF CEREBRO-
SPINAL FLUID TO BLOOD SUGAR IN FASTING STATE AND ONE AND
A HALF HOURS AFTER 0.5 GM. GLUCOSE PER KILO. OF BODY WEIGHT
GIVEN INTRAVENOUSLY

FASTING STATE			1½ HOURS AFTER 35 C.C. 20 PER CENT. GLUCOSE INTRAVENOUSLY		
BLOOD SUGAR MG.M. PER CENT.	C.S.F. SUGAR MG.M. PER CENT.	RATIO OF C.S.F. TO BLOOD SUGAR	BLOOD SUGAR MG.M. PER CENT.	C.S.F. SUGAR MG.M. PER CENT.	RATIO OF C.S.F. TO BLOOD SUGAR
95	61	0.64	105	87	0.82

fluid sugar to blood sugar was 0.64. An hour and a half after the intravenous injection of 35 c.c. of twenty per cent. glucose in saline the blood sugar was 105 mgm. per cent. and the cerebrospinal fluid sugar 86 mgm. per cent., giving a ratio of 0.82. From this experiment it seems probable that variations in the ratio of cerebrospinal fluid to blood sugar are dependent on variations in

the blood sugar content and delay in their manifestation in the cerebrospinal fluid.

Tuberculous meningitis.—All investigators report a reduced spinal fluid sugar in tuberculous meningitis and the majority mention that this value varies with the stage of the disease. Neale and Esslemont (1928) quote several cases in which there was complete absence of sugar, a finding which is confirmed by Bokay (1929). Mogilnicki (1930), on the other hand, states that it is never completely absent and Soedjono's (1938) results support this. Nissen (1937) quotes 40 mgm. per cent. as the lower limit of normal cerebrospinal fluid sugar and finds that ninety-one per cent. of his tuberculous cases yield values below 30 mgm. per cent., whilst Tcherkassov and Jolkver (1935) find the majority (sixty-one per cent.) of their results under 20 mgm. per cent. These last three observers mention the finding of a raised blood sugar in the later stages of the disease. The findings from the literature are shown in table 5.

TABLE 5
THE CEREBROSPINAL FLUID SUGAR CONTENT IN TUBERCULOUS MENINGITIS

OBSERVER	C.S.F. SUGAR IN MGM. PER CENT.			
			MAXIMUM	MINIMUM
Neale and Esslemont (1928)	72	0
Mogilnicki (1930)	36	8
Soedjono (1938)	75	10
Tcherkassov and Jolkver (1935)	20	—
Nissen (1937)	30	—
Hendry (present series)	86	5

As regards the variations in cerebrospinal fluid sugar level during the course of the disease, Soedjono (1938) quotes four distinct phases : (a) when there is a gradual fall in cerebrospinal fluid sugar to 18 or 20 mgm. per cent. ; (b) a few days during which the value fluctuates between 10 and 40 mgm. per cent. ; (c) a rise to normal limits of 50 to 65 mgm. per cent. ; and (d) a repetition of phase (b).

No blood sugar estimations are given for comparison. Weichsel and Herzger (1936) regard diminution in cerebrospinal fluid sugar as a diagnostic sign occurring twenty-five to thirty days before death. This decrease follows the rise in globulin and the increase in cell count. They find that about two weeks before death, there may be a slight increase in sugar content before the final drop to 10–20 mgm. per cent. and give the ultimate ratio of cerebrospinal fluid sugar to blood sugar as 0·12–0·08.

Mogilnicki (1930) in reviewing seventy-two cases, attributes the finding of a high blood sugar content to the occurrence of convulsions. These, after a time lag, raise the cerebrospinal fluid sugar value, and, as will be seen later, such cases furnish a cerebrospinal fluid sugar well within normal limits and emphasize the necessity for withdrawing blood as nearly as possible at the same time as the cerebrospinal fluid in order to obviate misinterpretation of an unexpectedly high cerebrospinal fluid sugar content.

In the present investigation twenty-eight cases of tuberculous meningitis have been studied in children whose ages ranged from four months to eight and

a half years. On an average, the blood and cerebrospinal fluid were examined every two or three days. In a few cases one estimation only was carried out, the children being in a late stage of the disease when admitted to hospital and dying before a second examination could be made. In the cases in which more than one estimation was possible the longest interval between the first and the last was twenty-two days and the shortest one day. This difference in time between first and final findings must be borne in mind, as, in the cases in which the interval is short, both estimations represent the condition in the late stage of the disease, whilst, in the cases in which there is a considerable interval, the first estimation represents the condition at an early stage and the last at a late stage. In table 6 the initial and final blood sugar and cerebrospinal fluid sugar values are shown.

TABLE 6
THE CEREBROSPINAL FLUID AND BLOOD SUGAR IN TUBERCULOUS
MENINGITIS

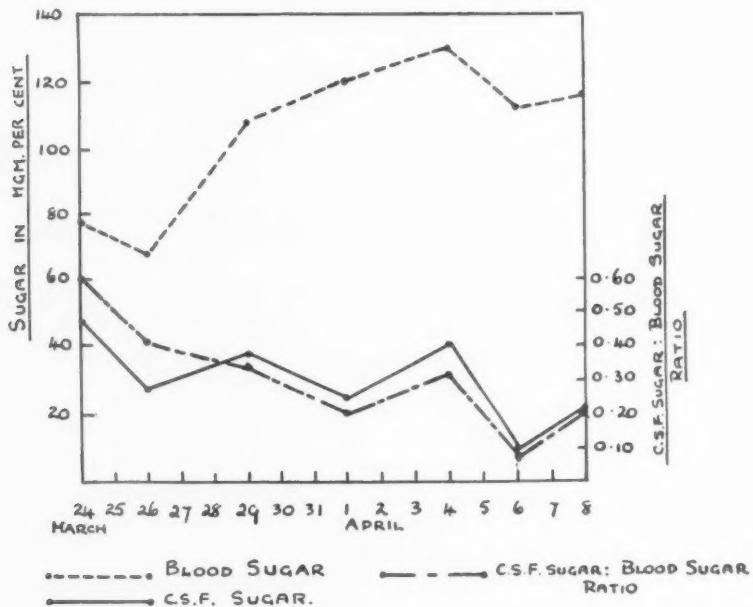
NAME	FIRST ESTIMATIONS			TIME INTERVAL IN DAYS	FINAL ESTIMATIONS			
	SUGAR IN MGM. PER CENT.		RATIO OF C.S.F. SUGAR TO BLOOD SUGAR		SUGAR IN MGM. PER CENT.		RATIO OF C.S.F. SUGAR TO BLOOD SUGAR	
	BLOOD	C.S.F.			BLOOD	C.S.F.		
M.I. . .	—	7	—	8	73	22	0·30	
A.A. . .	77	14	0·18	—	—	—	—	
K.K. . .	143	36	0·25	—	—	—	—	
M.M. . .	105	27	0·24	3	84	32	0·38	
J.G. . .	87	20	0·23	1	75	11	0·14	
P.R. . .	74	22	0·27	—	—	—	—	
A.McR. . .	93	63	0·67	—	—	—	—	
C.B. . .	50	12	0·24	1	89	20	0·22	
V.M. . .	106	35	0·32	4	190	30	0·16	
M.McM. . .	88	24	0·27	2	175	34	0·13	
P.S. . .	100	24	0·23	3	87	10	0·11	
J.B. . .	75	18	0·21	4	63	14	0·22	
S.D. . .	78	47	0·60	15	116	24	0·20	
R.McN. . .	274	86	0·31	14	85	16	0·18	
J.H. . .	78	14	0·18	4	85	36	0·42	
J.McG. . .	123	36	0·29	3	70	13	0·17	
M.McG. . .	128	37	0·28	22	127	12	0·08	
A.N. . .	—	15	—	13	—	17	—	
C.D. . .	75	16	0·21	3	83	11	0·13	
W.B. . .	83	27	0·32	6	68	14	0·20	
M.S. . .	—	12	—	3	83	5	0·06	
D.McK. . .	76	19	0·24	—	—	—	—	
E.H. . .	76	12	0·16	4	87	8	0·09	
M.L. . .	120	58	0·47	—	—	—	—	
W.L. . .	67	8	0·12	1	51	11	0·21	
R.C. . .	91	13	0·14	2	83	6	0·07	
A.A. . .	72	6	0·08	2	109	15	0·14	
A.McD. . .	68	21	0·30	5	108	20	0·18	

Taking a sugar concentration in the cerebrospinal fluid of 50 mgm. per cent. as the lower limit of normality, twenty-five of the twenty-eight cases showed

initial values below normal, and taking 0·60 as the lower limit of the ratio of cerebrospinal fluid sugar to blood sugar, twenty-three of the cases showed a ratio below this figure at the first examination. In twenty-two of the cases the blood and cerebrospinal fluid sugar was estimated more than once, and in the final examinations of these, which were in each case made within one or two days of death, all gave a cerebrospinal fluid sugar concentration of less than 50 mgm. per cent. and a ratio of cerebrospinal fluid sugar to blood sugar of between 0·06 and 0·42. In fourteen of these cases the ratio of cerebrospinal fluid sugar to blood sugar had fallen between the first and last estimations. Fig. 1 illustrates the progressive fall in the cerebrospinal fluid sugar content

FIG 1

CASE OF TUBERCULOUS MENINGITIS SHOWING THE RISING BLOOD SUGAR CONTENT, THE FALLING CEREBRO-SPINAL FLUID SUGAR CONTENT AND THE DIMINISHING CEREBRO-SPINAL FLUID SUGAR: BLOOD SUGAR RATIO AS THE DISEASE ADVANCES.



and the diminishing ratio of cerebrospinal fluid sugar to blood sugar in a typical case. Of the three cases which showed a normal cerebrospinal fluid sugar value two gave a ratio of cerebrospinal fluid sugar to blood sugar of less than 0·60, suggesting that the relatively high sugar content of the cerebrospinal fluid was due to disturbance in the blood sugar concentration.

This is well exemplified in the case of R.McN., a child aged two and a half years who, on admission to hospital, did not show signs typical of meningitis. He had been having continuous convulsions for one and a half hours before admission and a lumbar puncture was performed half an hour later. The

cerebrospinal fluid sugar was 86 mgm. per cent., a figure well above the normal value and, as an isolated observation, a strong point against the case being one of meningitis, but the blood taken at the same time gave a sugar concentration of 274 mgm. per cent. and the ratio of cerebrospinal fluid sugar to blood sugar was 0·31. In this case, hyperglycaemia induced by the convulsions had led to a marked and misleading increase in the concentration of sugar in the cerebrospinal fluid, but in spite of this, the ratio of cerebrospinal fluid sugar to blood sugar lay well below the normal limit.

Of the two cases which gave a ratio of 0·60 or over, one with a ratio of 0·67 died before a second estimation could be made, but the other, with an initial ratio of 0·60 showed a ratio of 0·41 on the second examination and of 0·20 fifteen days subsequent to the first examination. The results from this case are shown in fig. 1.

In the majority of cases a cerebrospinal fluid sugar concentration below 50 mgm. per cent. is strong presumptive evidence of meningitis, but a high finding must be viewed with caution unless a concomitant blood sugar estimation is carried out, for variations in this have an influence on the cerebrospinal fluid sugar content. The ratio of cerebrospinal fluid sugar to blood sugar is always below normal and is therefore of greater diagnostic value.

Purulent meningitis.—Most workers are agreed that in the early stage of purulent meningitis, the cerebrospinal fluid sugar is in small amount or completely absent.

Levinson and Cohn (1936) reporting five cases of meningococcal meningitis, examined before injection of serum, found cerebrospinal fluid sugar values ranging from zero to a maximum of 23 mgm. per cent. with an average of 9 mgm. per cent. Three cases of influenzal and five of streptococcal meningitis showed absence of sugar. Ford (1937) mentions a cerebrospinal fluid sugar of 10 mgm. per cent. or less. Neale and Esslemont (1928) find an initial low reading with some fluctuations from day to day until recovery when the cerebrospinal fluid sugar rises to the normal level. In two fatal cases it disappeared entirely. Soedjono (1938) remarks on a constant fall in the cerebrospinal fluid sugar in purulent meningitis and a low content which is most marked shortly before death.

Fourteen cases of meningococcal meningitis have been studied, and the blood and spinal fluid sugar levels found on admission are set out in table 7. None of the cases received serum; all were treated with prontosil. From this it will be seen that the cerebrospinal fluid sugar concentration ranged, on admission, from 0·52 mgm. per cent., with an average of 15 mgm. per cent. The ratio of cerebrospinal fluid sugar to blood sugar varied from 0·08–0·48 with an average of 0·19. If recovery took place, the sugar content slowly increased and after a varying period, usually less than a week, ran its normal parallel course to the blood sugar. The latter is usually raised in the first stage of the disease as at this time convulsions commonly occur. Fig. 2 illustrates a typical case in which recovery took place. One case of pneumococcal, two of *B. coli* and two of influenzal meningitis were also investigated. The children were all critically ill and died soon after admission. The sugar content of the cerebrospinal fluid was reduced to zero in every case.

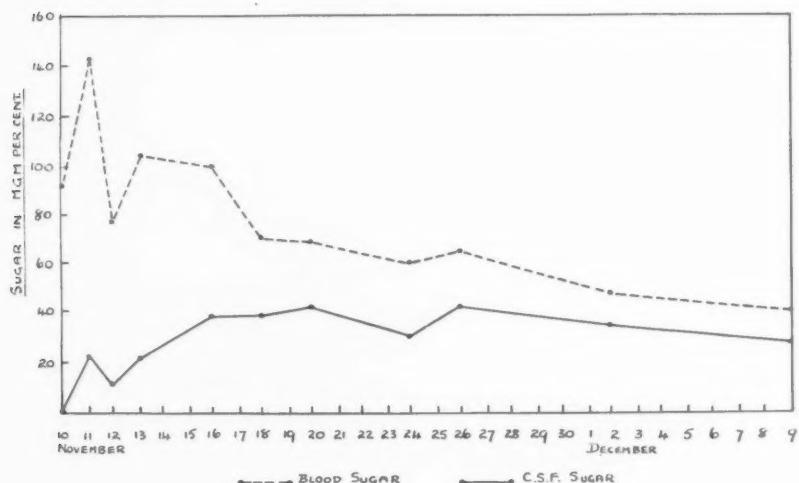
TABLE 7

THE BLOOD AND CEREBROSPINAL FLUID SUGAR AND CHLORIDE CONTENT DURING THE ACUTE STAGE OF MENINGOCOCCAL MENINGITIS

NAME	BLOOD SUGAR MGM. PER CENT.	C.S.F. SUGAR MGM. PER CENT.	RATIO OF C.S.F. SUGAR TO BLOOD SUGAR	BLOOD NaCl MGM. PER CENT.	C.S.F. NaCl MGM. PER CENT.	RATIO OF C.S.F. NaCl TO BLOOD NaCl
B.T. ..	84	35	0.41	465	716	1.54
A.M. ..	—	10	—	379	616	1.62
M.H. ..	91	Absent	—	363	640	1.49
J.F. ..	80	10	0.12	414	616	1.48
M.L. ..	63	12	0.19	517	643	1.24
A.W. ..	111	52	0.46	413	610	1.47
I.S. ..	—	12	—	—	646	—
T.F. ..	53	17	0.32	445	635	1.42
J.F. ..	113	10	0.08	476	648	1.36
M.G. ..	69	Less than 5	0.08	427	585	1.36
R.I. ..	65	Less than 5	0.08	338	623	1.83
M.F. ..	125	5	0.04	395	640	1.64
A.H. ..	91	44	0.48	366	630	1.72
T.M. ..	65	Less than 5	0.08	498	630	1.28

FIG 2.

CASE OF MENINGOCOCCAL MENINGITIS SHOWING THE FALL IN THE BLOOD SUGAR CONTENT AND THE RISE IN THE CEREBRO SPINAL FLUID SUGAR CONTENT AS RECOVERY TAKES PLACE



As a demonstration of the value of estimating the cerebrospinal fluid sugar and, in particular, the ratio it bears to the blood sugar for differential diagnosis, the following cases may be mentioned.

Case 1.—J.H. was a case of abdominal tuberculosis. On account of persistent nuchal rigidity in addition to the other clinical findings, he was lumbar punctured five times between the onset of the stiffness of the neck and death nine days later. The blood and cerebrospinal fluid findings are shown in table 8. From this it will be seen, that with the exception of the results on

May 22, 1938, the cerebrospinal fluid sugar content and percentage ratio were within normal limits. No meningitis was found on post-mortem examination.

TABLE 8
BLOOD AND CEREBROSPINAL FLUID SUGAR CONTENT IN A CASE OF
ABDOMINAL TUBERCULOSIS SUSPECTED OF HAVING MENINGITIS

DATE	BLOOD SUGAR MGM. PER CENT.	CEREBROSPINAL FLUID SUGAR MGM. PER CENT.	RATIO OF C.S.F. SUGAR TO BLOOD SUGAR
16.5.38	92	70	0.75
19.5.38	78	66	0.84
20.5.38	112	98	0.87
22.5.38	93	28	0.30
25.5.38	64	66	1.03

Case 2.—I.K. had hilum tuberculosis, and a history of vomiting, constipation, anorexia and listlessness raised the suspicion of meningitis. The cerebrospinal fluid sugar was 71 mgm. per cent., and the ratio of cerebrospinal fluid to blood sugar 0.90.

Case 3.—J.R. was a case of benign lymphocytic meningitis. Table 9 shows the blood and cerebrospinal fluid findings. In this case the diagnosis on admission was doubtful on clinical findings alone but the cerebrospinal fluid sugar content and the percentage ratio afforded strong evidence against its being a case of true meningitis.

TABLE 9
BLOOD AND CEREBROSPINAL FLUID SUGAR CONTENT IN A CASE
OF BENIGN LYMPHOCYTIC MENINGITIS

DATE	BLOOD SUGAR MGM. PER CENT.	CEREBROSPINAL FLUID SUGAR MGM. PER CENT.	RATIO OF C.S.F. SUGAR TO BLOOD SUGAR	CELLS
27.6.38	128	85	0.66	Lymphocytes
28.6.38	—	81	—	Lymphocytes
2.7.38	—	66	—	Lymphocytes
11.7.38	—	54	—	Lymphocytes
14.7.38	77	51	0.69	Lymphocytes

Two cases of anterior poliomyelitis were also examined. The results of sugar estimations on blood and spinal fluid are set out in table 10. In these two cases, as in case 3, the cerebrospinal fluid sugar content and the ratio of cerebrospinal fluid sugar to blood sugar were not reduced below the normal limits.

TABLE 10
BLOOD AND CEREBROSPINAL FLUID SUGAR CONTENT IN TWO
CASES OF POLIOMYELITIS

CASE	BLOOD SUGAR MGM. PER CENT.	C.S.F. SUGAR MGM. PER CENT.	RATIO OF C.S.F. SUGAR TO BLOOD SUGAR
1	54	50	0.92
2	153	137	0.96

Percentage of chlorides in blood and cerebrospinal fluid

Normal cases.—Most workers are agreed that, in adults, the normal chloride content of the blood varies between 450 and 600 mgm. per cent., and of the cerebrospinal fluid between 700 and 750 mgm. per cent. and that as a rule the results for children are similar, though Stewart (1928) gives 636–763 mgm. per cent. as the range for the cerebrospinal fluid chloride in the latter cases. Table 11 gives a few of the results of other workers. This shows that the normal blood chloride lies between 450–660 mgm. per cent. and cerebrospinal fluid chloride between 636–783 mgm. per cent.

TABLE 11
THE NORMAL VALUES FOR BLOOD AND CEREBROSPINAL FLUID CHLORIDE

OBSERVER		BLOOD NaCl MG.M. PER CENT.	C.S.F. NaCl MG.M. PER CENT.
Hawk and Bergein (1938)	450–500	—
Finkelstein and Merson (1934)	500–600	720–740
Soedjono (1938)	475–550	700–750
Stewart (children) (1928)	—	636–763
Neale and Esslemont (1928)	—	696–783
Hendry (children) (present series)	355–543	635–770

In the present investigation cerebrospinal fluid chloride and blood chloride were estimated in forty children who had no sign of meningeal involvement. The blood chloride was found to range from 355–543 mgm. per cent. and the cerebrospinal fluid chloride from 635–770 mgm. per cent. The low readings can be explained by the fact that many of these cases were dehydrated infants and children admitted with a history of vomiting, diarrhoea and convulsions and were lumbar punctured for diagnostic purposes. In every case in which the blood chloride was low, a lowered reading was also found in the cerebrospinal fluid. These results correspond with the findings of Finkelstein and Merson (1934), Linder and Carmichael (1928) and Nowika (1924) who hold that blood and spinal fluid chloride run a parallel course. In order to prove this from the present series, the ratio of cerebrospinal fluid chloride to the blood chloride was calculated in each case. This was found to range from 1·32–1·91 with a ratio of 1·60–1·65 in a third of the cases and the average at 1·59. As most of these cases were lumbar punctured once only, no serial figures are available.

Tuberculous meningitis.—Investigation of the literature on the chloride content of cerebrospinal fluid in tuberculous meningitis shows that most workers look on 500–690 mgm. per cent. as the expected range. All agree that there is a progressive diminution with the progress of the disease.

Nowika (1924), Linder and Carmichael (1928) and Fowweather (1930) believe that the low cerebrospinal fluid chlorides indicate a general reduction in body chlorides. Neale and Esslemont (1928) mention a general agreement

between the relative blood and cerebrospinal fluid chloride content but do not establish any strict ratio for meningitic or non-meningitic cases. Nissen (1937) finds that the values for cerebrospinal fluid chlorides and sugar tend to run parallel. From table 12 it appears that cerebrospinal fluid chloride in tuberculous meningitis may lie between 450 and 680 mgm. per cent.

TABLE 12
THE CEREBROSPINAL FLUID CHLORIDE CONTENT IN TUBERCULOUS MENINGITIS

OBSERVER	C.S.F. NaCl IN MGM. PER CENT.		
	MAXIMUM	MINIMUM	
Soedjono (1938)	600	450	
Fowweather (1930)	640	590	
Finkelstein and Merson (1934)	680	—	
Neale and Esslemont (1928)	673	500	
Hendry (present series)	757	543	

The present series comprises twenty-eight cases. In many of these the spinal fluid chloride was estimated on several occasions, but in table 13 only the first and last estimations are shown. From this it will be seen that on the first examination the chloride ranged between 689 and 549 mgm. per cent. and shortly before death between 757 and 561 mgm. per cent. The average ratio of cerebrospinal fluid chloride to blood chloride both in the early and in the late stage was 1·55. These identical average ratios, which correspond so closely to the average normal ratio of 1·59, strongly suggest that any reduction in the cerebrospinal fluid chloride content in tuberculous meningitis is not due to the meningeal condition, but to reduction of chloride in the blood. The fact that there is also reduction in the urinary chlorides strengthens this supposition. Reference to fig. 3 shows the course of blood and spinal fluid chloride and sugar content from a typical case and demonstrates the parallelism of the chloride throughout the disease in contrast to the ever increasing difference in the two sugar curves. Referring to the tables (6 and 13) showing the results of sugar and chloride estimations in blood and cerebrospinal fluid on admission and shortly before death, it will be noticed that, at the onset, a low cerebrospinal fluid sugar content and ratio is a much more constant finding than a lowered chloride content and a more satisfactory test from a diagnostic point of view.

Meningococcal meningitis.—In meningococcal meningitis, the chlorides are of little diagnostic value although prognostically their rise indicates the likelihood of recovery. Most workers find the cerebrospinal fluid chloride content diminished on admission, but to a lesser extent than in tuberculous meningitis. In the present series, the cerebrospinal fluid chloride on admission ranged from 716–585 mgm. per cent., the blood chloride from 498–338 mgm. per cent. and the ratio from 1·83–1·24 with an average of 1·41. This last value, as in tuberculous meningitis, approximates to the normal. Most cases showed a gradual rise in cerebrospinal fluid chloride content with clinical improvement,

a rise parallel to that of the blood chloride. This rise in the cerebrospinal fluid chloride content was never so dramatic as the increase in sugar content and often fluctuated from day to day without any apparent change in the clinical condition. Fig. 4 is a typical example. The ratio of cerebrospinal fluid chloride to blood chloride remained remarkably constant during the course of the illness in every case.

TABLE 13
THE CHLORIDE CONTENT OF THE BLOOD AND CEREBROSPINAL FLUID
IN TUBERCULOUS MENINGITIS

NAME	FIRST ESTIMATIONS			TIME INTERVAL IN DAYS	FINAL ESTIMATIONS			
	NaCl IN MGM. PER CENT.		RATIO OF C.S.F. NaCl TO BLOOD NaCl		NaCl IN MGM. PER CENT.		RATIO OF C.S.F. NaCl TO BLOOD NaCl	
	BLOOD	C.S.F.			BLOOD	C.S.F.		
M.I. . .	—	610	—	8	408	670	1.39	
A.A. . .	425	578	1.33	—	—	—	—	
K.K. . .	381	589	1.54	—	—	—	—	
M.M. . .	406	608	1.47	3	372	578	1.55	
J.G. . .	393	590	1.50	1	407	597	1.22	
P.R. . .	405	635	1.55	—	—	—	—	
A.McR. . .	371	625	1.55	—	—	—	—	
C.B. . .	343	568	1.65	1	345	586	1.69	
V.M. . .	391	666	1.65	4	409	716	1.75	
M.McM. . .	412	689	1.64	2	420	757	1.80	
P.S. . .	371	640	1.72	3	418	689	1.64	
J.B. . .	414	651	1.57	4	497	644	1.29	
S.D. . .	364	660	1.78	15	350	609	1.71	
R.McN. . .	421	647	1.53	14	423	599	1.41	
J.H. . .	388	690	1.55	4	365	585	1.60	
J.McG. . .	367	554	1.50	3	338	573	1.40	
M.McG. . .	408	635	1.55	22	359	600	1.66	
A.N. . .	—	689	—	13	—	543	—	
C.D. . .	361	593	1.66	3	371	636	1.71	
W.B. . .	491	662	1.34	6	391	658	1.68	
M.S. . .	—	595	—	3	404	626	1.54	
D.McK. . .	328	577	1.75	—	—	—	—	
E.H. . .	328	549	1.67	4	313	561	1.79	
M.L. . .	368	567	1.54	—	—	—	—	
W.L. . .	373	590	1.58	1	339	569	1.42	
R.C. . .	429	621	1.44	2	452	630	1.39	
A.A. . .	322	546	1.38	2	352	621	1.49	
A.McD. . .	388	556	1.43	5	—	566	—	

Other types.—Two cases of *B. coli*, two of influenzal and one of pneumococcal meningitis showed a similar reduction to that found in meningococcal meningitis.

Conclusions

1. In the normal subject variations in the cerebrospinal fluid sugar content are dependent on variations in the blood sugar level, but changes in the latter are not immediately reflected in the cerebrospinal fluid.

FIG. 3
TYPICAL CASE OF TUBERCULOUS MENINGITIS.

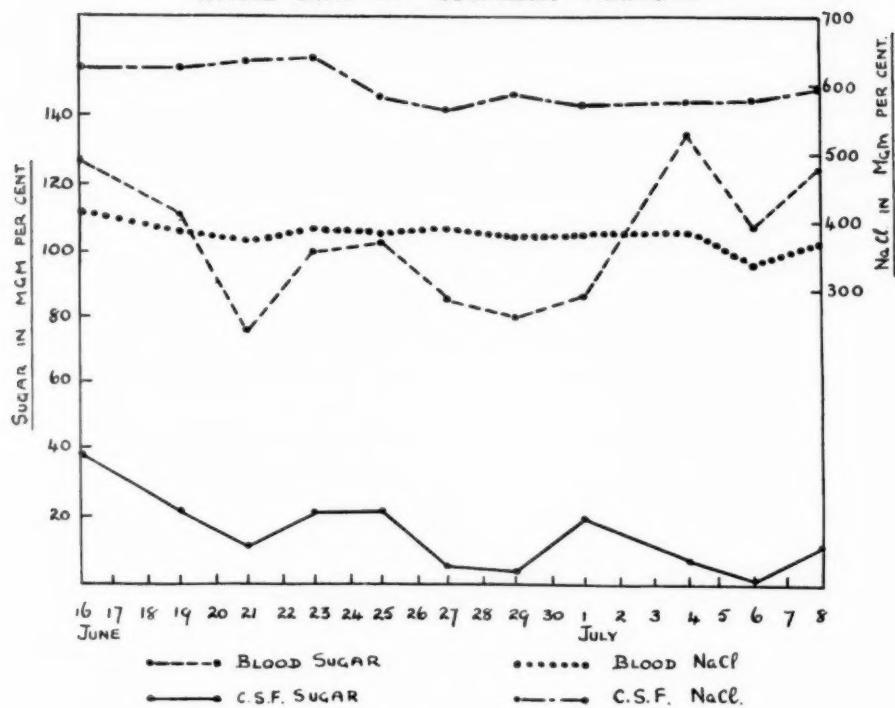
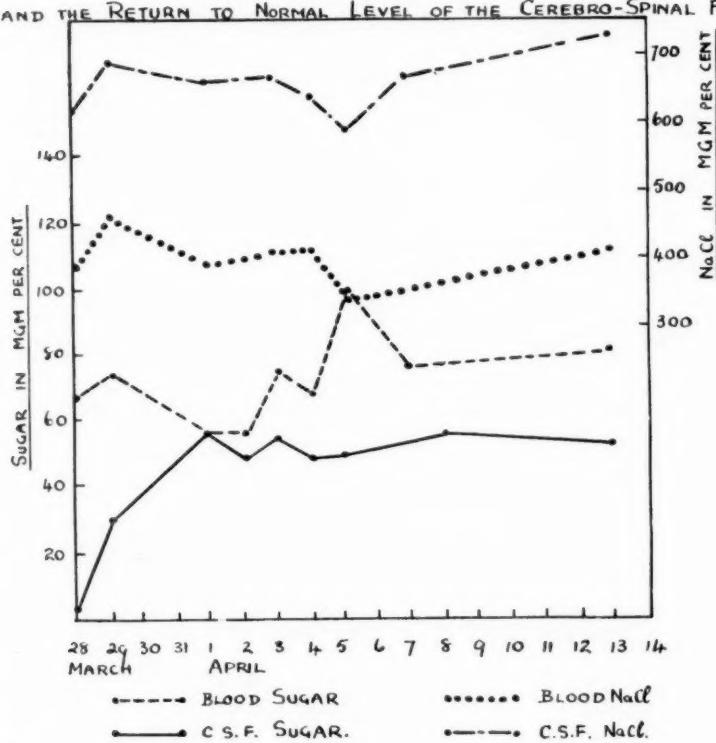


FIG. 4
TYPICAL CASE OF MENINGOCOCCAL MENINGITIS SHOWING THE
PARALLEL COURSE OF THE BLOOD AND CEREBRO-SPINAL FLUID CHLORIDES
AND THE RETURN TO NORMAL LEVEL OF THE CEREBRO-SPINAL FLUID SUGAR



N*

2. The lower limit for cerebrospinal fluid sugar content in normal cases is 50 mgm. per cent. and the ratio of cerebrospinal fluid sugar to blood sugar 0·6.

3. In tuberculous meningitis, the cerebrospinal fluid sugar content is reduced as is also the ratio of cerebrospinal fluid sugar to blood sugar; the reduction in both becomes more marked as the disease progresses. If convulsions occur, the cerebrospinal fluid sugar level may be raised to apparently normal limits, but the blood sugar is also raised and the ratio of cerebrospinal fluid sugar to blood sugar remains below normal.

4. In meningococcal meningitis, the cerebrospinal fluid sugar is reduced and may be almost entirely absent and the ratio of cerebrospinal fluid sugar to blood sugar is below normal. As recovery takes place, the cerebrospinal fluid sugar content and the ratio of cerebrospinal fluid sugar to blood sugar return to normal.

5. The cerebrospinal fluid chloride content is reduced in all forms of meningitis but this is due to a reduction in the blood chloride content.

6. Chloride reduction in the early stages of tuberculous meningitis is less constant than reduction in the cerebrospinal fluid sugar content.

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EUMYDRINE IN PYLORIC STENOSIS

BY

H. ST. H. VERTUE, D.M.

The treatment of pyloric stenosis by eumydrine was introduced by Svensgaard in 1935. Sixty-one cases were treated, with controls. The immediate results were diminished period of vomiting, shortened stay in hospital and better increment in weight. Braithwaite (1937) gave a brief report of twenty-two cases, of which eighteen were successful and four relieved by surgery. This paper gives an account of eumydrine, of experience of the drug at welfare centres and of results of its use in Guy's Hospital. When it was virtually completed an article on the treatment of pyloric stenosis by eumydrine by Dobbs (1939) appeared, to which reference is made later.

Physiology

In pyloric stenosis of infancy there is an interference with the normal opening of the pylorus ; food leaves the stomach with difficulty and some of it is vomited ; the pylorus is hypertrophied and may be palpable ; gastric peristalsis is visible. Atropine is known to be beneficial in relieving the spasm of the sphincter ; eumydrine, chemically related to atropine, is much more successful, but the mode of action of neither drug is quite clear.

The opening of the pylorus has been studied by McSwiney and Pyrah (1932) in dogs. The sphincter is normally closed. When a wave of contraction starts in the pyloric antrum the sphincter relaxes and remains open for five to six seconds. About a second before the wave reaches its summit the sphincter closes again and stays closed during the remainder of this wave and afterwards until the next. These movements are governed by the intrinsic nervous system. The opening and closing can be influenced by local events. Serdjukow (Pawlow, 1902) produced closure of the pylorus by introducing acid into the duodenum and relaxation by increasing acidity in the stomach. This action is independent of the central nervous system. In time clinicians became aware that acidity of contents is not of great importance, because persons with achlorhydria may yet have a normal emptying time. McSwiney and Spurrell (1933) found the osmotic pressure of the gastric contents was more important. Hypertonic meals cause delay in emptying, and hypotonic leave more quickly than isotonic. Spurrell (1935) found that alterations in the pressure of the duodenal contents affected the rate of emptying. Using cats he observed that with a duodenal pressure of 10 cm. of water, 60 c.c. of saline were evacuated in five to ten minutes, but when the pressure was raised to 30 cm. the rate of outflow was halved. He attributed this reflex to the splanchnic nerves, since in his preparation the intrinsic nerves are divided. Section of the vagi had no effect.

The stomach with its double nerve supply, vagal and sympathetic, can be influenced by other viscera, by the central nervous system, and even by the

brain, since the sympathetic depends on nuclei in the hypothalamus. The actions of the vagi and sympathetic have been reviewed by McSwiney (1931). Section of vagi causes diminished tone, slow peristalsis and delayed emptying. Stimulation usually causes dilatation of the pyloric sphincter and increase in tone and movement of the stomach ; but if the stomach is already in a state of high tonus the result is the opposite. The vagus, in short, is predominantly motor to the stomach and dilator to the sphincter ; but the effect is not pure. Stimulation of the splanchnic nerves causes the body to relax and the sphincter usually to contract ; but if the sphincter is already hypertonic it relaxes. What happens when either of these nerves is stimulated depends not only on which nerve it is but also on the state of the stomach. One nerve under the right conditions will do what the other does under other conditions. These mixed effects are not due to mixture of fibres, according to Spurrell, but to overlapping of functions. When consideration is given as to which nerve might be responsible for a spasmodic closure of the sphincter in pyloric stenosis and be paralysed when the spasm is relieved by atropine or eumydrine, there are difficulties. It seems that the end-organs that cause closure of the pylorus can be excited by a great variety of stimuli and can be influenced by both the sympathetic and the vagus, and by the intrinsic nerves, but predominantly by the sympathetic. Supposing that there are such influences descending to one or other of these nerves, whence do they come ? There seems no answer yet to this question except the rather far-fetched idea that pyloric stenosis is a disease of the same order as asthma, dependent in part on the personality of the patient. That these patients often have a particular kind of personality, masculine, vigorous and alert, is generally recognized. But is there a genuine spasm of the pyloric sphincter at all ? Doubt has even been thrown on this.

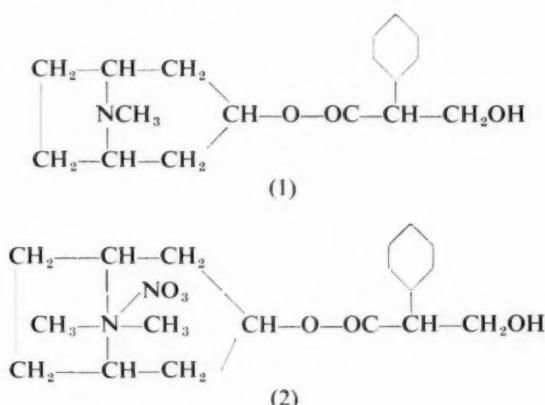
Achalasia.—This is a condition in which the cardiac sphincter fails to open, coming on later in life and said to be due to degeneration of Auerbach's plexus (Hurst, 1924). It might be supposed by analogy that pyloric stenosis was a condition in which the pyloric sphincter failed to open in infancy owing to delayed development of the appropriate nerve fibres. But there is one striking difference that seems to preclude the idea ; the cardiac sphincter is never hypertrophied, whereas the pyloric sphincter is prominently so. The one is merely not relaxed, the other actively and abnormally constricted—or so it seems ; but according to Cameron (1926) it is not the sphincter that is hypertrophied at all, but something else, namely the pyloric canal. This he describes as part of the expelling apparatus of the stomach, not of the retaining : a long, cylindrical tube of circular muscular fibre, thickened from abnormal effort to push the stomach contents past a passively closed sphincter (Cameron, 1926). This view, he says, is in keeping with clinical and radiographical evidence. It seems also to fit in well with the naked-eye appearance of the stomach. It has the merit of simplicity and it makes the actions of atropine and eumydrine fairly comprehensible, though not more so than the spasmodic view.

Pharmacology

Atropine has a general paralytic effect on nerve endings in the stomach. McCrae and Macdonald (1928) studied the effect of atropine given intravenously to cats. There was a general relaxation of the stomach, with fall in intra-gastric pressure, arrest of all movements for at least four hours and absence of response to stimulation of any nerve. No mention was made of special effect on the pyloric sphincter. Previous observers (cited by them) obtained results that were in all important respects the same. The dose of atropine given to a child is smaller than that used in these experiments (0.05 mgm. against 0.1 to 0.15 mgm.) and it is given by mouth. The effects therefore may not be quite

the same. Visible peristalsis, for instance, is not abolished, but goes on at least for a time. If pyloric stenosis is a spasm of the sphincter, then medicinal doses of atropine which are beneficial must be blocking impulses to the sphincter without inhibiting peristalsis. But if it be an achalasia, then the general relaxation described, in which the sphincter presumably shares, is reached before peristalsis is abolished. The action of atropine as at present known throws little light on the cause of the disease ; but there is this to be considered : both atropine and eumydrine sometimes fail in their effect, even if the dose is increased. Is not the likely explanation of this that constrictor impulses are reaching the sphincter too powerful for the drug in medicinal dose to abolish ?

EUMYDRINE.—Atropine (1) is an ester formed from the base tropine and the acid tropic acid, with elimination of water. Tropine is both a tertiary base (amine) and a secondary alcohol. Its peculiar feature is the nitrogen bridge with methyl group attached. Tropic acid is phenyl hydracrylic acid. Tropine itself has no pharmacological action.



Numbers of substances have been tried in which other acids have been combined with atropine, of which the best known is homatropine, the compound with mandelic acid. Of the rest some are toxic and some inactive. Alteration in the attachments to the nitrogen bridge gives another variety of compounds. Demethylation, for instance, produces diminished activity. Noratropine, the substance formed, has one-eighth of the activity of atropine (Dyson, 1928). The reverse change can also be produced in the following way. Atropine can, like ammonia, add itself to acids ; in fact, it is usually administered as a sulphate on account of its much greater solubility. The nitrogen atom has now become quinquevalent instead of trivalent. One of the extra valencies takes up the acid and the other the hydrogen atom. This hydrogen atom can be substituted by a methyl group, so that there are now two attached to the nitrogen bridge : if the acid in combination at the same time is nitric acid, the result is eumydrine or atropine methyl nitrate (2).

Eumydrine was intended as a mydriatic. It is sometimes used when atropine irritates the eye ; but in this country it has not been well known. Svensgaard in her paper stated that it was one-fiftieth as toxic as atropine, but gave no particulars nor reference. Dyson is exiguous, but illuminating. He says that as a result of the chemical change from atropine to the dimethyl quaternary ammonium salt the action is diverted from the remainder of the nervous system to the peripheral nerve-endings (Dyson, 1928). This goes far to explain the superiority of eumydrine over atropine. It means that a larger dose can be given with a greater local effect and less danger of poisoning. In actual fact I have not seen eumydrine produce any effects at all except

locally ; there is neither mydriasis, rapid pulse, flushing, dry mouth, nor any other sign when it is given by mouth. It is unstable on solution ; perhaps it is quickly destroyed on absorption.

Experience of eumydrine

The patients for whom eumydrine was used were seen at welfare centres, which means that they should have been, and actually were, caught early and treated promptly. Most were treated in the observation wards of the Borough of Poplar, where good nursing greatly helped towards success. I was also fortunate in having six mothers out of seven of exceptional merit, and a seventh who was at least of average goodness. Furthermore six out of the seven babies were breast-fed. In these circumstances the drug acted excellently. In not less than forty-eight hours vomiting had begun to diminish, the weight ceased to fall, pain grew less and sleep and contentment took its place. The visit to the first child two days after admission showed dramatic improvement which was steadily maintained. No relapses occurred in any of the seven cases ; there were no signs of toxicity and no after-effects of the illness. Reviewed at four months, the patients appeared a perfectly normal set of children (except for the undernourished condition of the child of the least satisfactory mother, who was beginning bottle feeding). The time spent in the wards was curtailed as experience was gained, and in the end two children were actually treated as out-patients with success. It is not contended, however, that severe cases might not still require operation, especially if they escaped observation until too late.

The dose of the drug was the same as that used by Svensgaard, namely 0.25 mgm. given half an hour before each feed, dissolved in one drachm of water ; but five feeds a day and not seven were given. Fresh solutions were made up weekly. The criteria of the disease were projectile vomiting, visible gastric peristalsis, constipation and loss of weight. Distinction between pyloric stenosis and pyloric spasm appears meaningless nowadays.

Case reports

R.B. showed characteristic rise of weight at the beginning of her life, followed by a fall when symptoms began in the fifth week. After two days of vomiting the baby was brought to the welfare centre and gastric peristalsis was easily visible, accompanied by obvious discomfort. The baby was admitted at once. Vomiting was projectile and occurred at least once after every feed. The bowels were not opened for five days. Eumydrine was begun at once. For twenty-four hours there was little change in the child and a further slight fall in weight. But in forty-eight hours vomiting had much diminished, weight had begun to rise and the whole aspect of the child had altered for the better. On the fourth day the weight lost was regained, on the sixth vomiting ceased altogether, and on the tenth peristalsis was last observed. She was discharged on the nineteenth day. Treatment was stopped in six weeks. This child was the only female and she was breast-fed.

F.W.—Vomiting began in the fourth week, seven days before admission. There was a loss in weight of 18 oz. There was much pain after food, copious vomiting and vigorous peristalsis. Improvement began with arrest in the fall

of weight on the third day after treatment. On the fourth there was a sharp rise with dramatic remission of symptoms. The last vomit occurred on the eleventh day and the patient was discharged on the thirteenth. The previous weight was regained on the twentieth day. Peristalsis was visible for five weeks. The drug was withdrawn at the ninth week, but vomiting started again and it was administered until the thirteenth week. This was a vigorous breast-fed baby with an exceptionally good mother, who recognized the nature of the disease, having seen it in a nephew.

R.S.—Vomiting began in the fourth week. The mother was prompt and brought her baby for admission after two days. The amount of weight lost was doubtful, as he had not been weighed for a fortnight. The weight at birth was 6 lb., and in the fourth week 5 lb. 15 oz. The usual symptoms were present and the peristalsis was obviously painful. This early case was promptly relieved. Projectile vomiting actually stopped in twenty-four hours and all vomiting in seven days. He was discharged after twelve days. Eumydrine was administered for thirteen weeks. He was a slightly small but otherwise normal breast-fed baby.

B.B. had been sick since birth, but between the third and fourth weeks the vomiting became worse. He lost twelve ounces and passed no faeces for eight days. Peristalsis of considerable intensity with pain was easily seen. Vomiting was projectile. Improvement was rapid. In forty-eight hours there was a substantial gain in weight. Vomiting became less forcible and frequent. After seven days it stopped altogether. He was discharged on the seventh day; weight was regained by the twelfth day. Eumydrine was administered for eleven weeks. Peristalsis was active for some time, but disappeared after eight weeks. He was a lusty breast-fed baby.

A.B. was the only bottle-fed baby. For five weeks after birth he did well. He began to vomit in the sixth week and had lost 10 oz. in weight by the eighth. There were forcible vomiting, visible peristalsis with crying and constipation. After eumydrine was given vomiting stopped in three days. The baby was discharged in seven days and regained his weight in ten days. Eumydrine was given for sixteen weeks. He was fed on a preparation of lactic acid milk. He became perfectly healthy and normal.

TABLE I

	HISTORY, LENGTH (DAYS)	WEIGHT LOST (OUNCES)	DAYS TAKEN TO REGAIN WEIGHT	DAYS TAKEN TO CEASE VOMITING	DAYS IN HOSPITAL	EUMYDRINE ADMINISTRATION (WEEKS)	WEIGHT AT 4 MONTHS MORE OR LESS THAN AVERAGE (OUNCES)
R.B.	3	6	4	6	19	6	+ 8
F.W.	7	18	20	11	13	13	+34
R.S.	2	not known	—	7	12	13	- 5
B.B.	indefinite	12	12	10	7	11	+22
A.B.	21	10	10	3	7	16	-20
L.D.	4	1	4	4	—	13	+16
H.K.	5	not known	—	5	—	9	-40
Aver- age Svens- gaard	7	8	10	7	8	11	+ 2
			7	21	69		

L.D.—No symptoms occurred until the third week. The baby was sick for three days ; on the fourth day he was seen and found to have projectile vomiting, and visible peristalsis with squirming movements. He had lost 1 oz. He was in such good condition that it was decided to try out-patient treatment at the Royal College of St. Katharine, Poplar. He vomited for four days after treatment, at first copiously, then only once or twice a day. After that he did not vomit again. Peristalsis was visible for five weeks, eumydrine being given for thirteen weeks.

H.K.—His mother reported that his vomit was sufficiently forcible to shoot across a railway carriage. He was seven weeks old when seen, and the history dated back five days. He weighed only 7 lb. 12 oz., but as he had not been weighed since birth it was impossible to say how much he had lost. Peristalsis and constipation were noted. He was not desperately ill and as his mother was an intelligent woman of the professional class it was decided to try treatment at home. Vomiting stopped five days after treatment and there was a gain of 3 oz. in the first week. The child was much quieter and happier. Eumydrine was continued for nine weeks and there was no relapse. But she did not do very well with him and lost her breast-milk.

Results in Guy's Hospital

It was Dr. H. C. Cameron's successful use of the drug in Guy's Hospital that first prompted me to try it. He had kindly allowed me to examine the results of his treatment there (eleven cases). There are also three who were under the care of Dr. Ellis, which I have his kind permission to include, making a total of fourteen. Scrutiny of the reports shows that the criteria of what constitutes pyloric stenosis were the same as those I adopted. The methods of treatment and dosage (0.25 mgm.) were exactly the same, except that in two instances for a short time the dose was increased to 0.5 mgm. There is one difference, namely in the time that elapsed between onset and treatment. On an average it is more than two-and-a-half times as long in the hospital cases as in the welfare cases. The reason for this is quite obvious. Naturally the patients were also longer in hospital, more than twice as long. Supporting treatment was needed in four cases, that is saline infusions and blood transfusions. There is one death to record, from bronchopneumonia. It would be unjust to blame either the treatment or the disease itself, since all vomiting had stopped for a week, weight had increased by three hundred grammes and the patient's progress was satisfactory when the infection occurred. He was one of those, in fact, who came into hospital with one disease and died of another. Minor points to mention were that two were females and a surprisingly small number were breast-fed, only three children wholly and two partially. The favourite substitute was lactic acid milk.

In spite of the disadvantages of a comparatively late start and of much bottle-feeding, the treatment was highly successful. There are no failures to record. Vomiting was controlled in the same average number of days (seven) as in my own easier series. The longest time was thirty-six days and the shortest one day. It is unfortunately not possible to compare the regaining of weight. Nothing is known of the weight of these children at the time when symptoms began. It is only possible to record how long they took to regain

their weight on admission ; this was seven days. No signs of toxicity were recorded. Complications or, better, intercurrent infections occurred twice ; an otorrhoea and the aforesaid bronchopneumonia.

Judged by these twenty-one cases in all, administration of eumydrine is a rapid, harmless and successful method of relieving the pyloric stenosis of infancy. Its introduction, apparently by Svensgaard, has been a genuine advance in medical treatment.

TABLE 2
GUY'S HOSPITAL SERIES

Number	14	Vomiting abolished, days (average)	7
Days in hospital (average)	18	Death (bronchopneumonia) .. .	1
History of vomit, days, (average) .. .	19	Surgery	nil

Before concluding some reference may be made to the recent paper by Dobbs (1939) describing twenty cases in University College Hospital and elsewhere. My paper was written independently of his ; but the description of the successful use of the drug, the results obtained and the conclusions drawn are corroborative. On the whole the results at University College Hospital were a little less favourable than those we reported, since surgical intervention was resorted to in three cases and there was one death, not from intercurrent infection but from paralytic ileus, which was attributed to the eumydrine itself. Somewhat larger doses were usual (0.3 mgm.) ; and treatment was delayed from twelve to eighteen hours after admission. The general practice at Guy's Hospital was to begin at once. Dobbs also resorted to saline infusions as a routine, which was not found necessary in the present series except as stated.

Conclusions

1. Eumydrine causes relaxation of the gastric musculature. It has a pronounced local and an insignificant general effect.
2. It relaxes the pylorus in pyloric stenosis of infancy.
3. It is a safe, rapid and successful remedy for this condition.
4. Success is uniform in the present series, but may not always be so.
5. Vomiting is abolished in most cases within seven days.
6. Weight is regained in most cases within eight days.
7. Stay in hospital can generally be short ; mild cases can be treated as out-patients.

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OSSEOUS DYSTROPHY FOLLOWING ICTERUS GRAVIS NEONATORUM:

GENERALIZED OSTEITIS FIBROSA WITH AREAS OF PIGMENTATION OF THE SKIN AND PRECOCIOUS PUBERTY IN THE FEMALE

BY

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Since the institution of the treatment of icterus gravis neonatorum with adult blood a number of babies so affected have survived. The extent to which physical and mental defects occur in these survivals and the relationship of the defects to the primary illness—whether consequent or merely concomitant—present problems of great interest and of considerable practical importance.

The development of osseous dystrophy in one such case has already been reported (Braid, 1932). That occurred in a male child in whom the jaundice was associated with acholia and in whom pathological pigmentation of the skin was present. The hypothesis then offered was that a function of the liver concerned with the storage and utilization of vitamins had been damaged during the period of jaundice and that the disturbance of bone growth had thereby ensued. McCune and Bruch (1937) published a case of 'osteodystrophia fibrosa' in a female child who suffered from icterus gravis associated with acholia, who had pathological pigmentation of the skin and developed signs of hyperthyroidism and precocious puberty. Albright and his colleagues (1937, 1938) record in seven cases a 'syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction in the female.'

These eight cases present a striking similarity to my original patient, who is now ten years old. He has been under observation at frequent intervals, when previous investigations have been repeated and liver function has been tested. These are now recorded along with notes of a second case, a female now aged two years who had icterus gravis neonatorum associated with acholia, who has extensive pigmentation of the skin and who has developed an osseous dystrophy similar to that in the first case. For access to this second case I am indebted to Professor Parsons.

Case reports

Case 1.—R. T., male, was born at home on November 5, 1928. He was the second child of healthy parents and at birth weighed 7 lb. 10 oz. His mother was quite well throughout the pregnancy and her first child had always been healthy. About the second day he became jaundiced and on the tenth day he bled profusely from the mouth and umbilicus, and on that account he was admitted to the nursery at the Maternity Hospital. When first seen he looked extremely ill, was deeply jaundiced and bleeding freely. A single dose of whole



FIG. 1.—Patient on October 13, 1932.



FIG. 2.—Patient on January 4, 1934.

blood given intramuscularly arrested the bleeding ; but for the next three weeks his condition remained critical and the weight fell to 5 lb. 9 oz. The jaundice was apparently stationary and the stools were consistently colourless. This obstructive type of jaundice is now a well-recognized feature of icterus gravis. On December 8 bile pigment was first detected in the stools. A gradual general improvement then set in and at the age of seven weeks he was able to go home, where he continued to make good progress. He was entirely breast-fed. The yellow staining of the skin persisted for many weeks, and probably on that account an extensive pigmentation of the right side of his face and neck and shoulder region was not noted till he was between four and five months old.

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The abnormality of his bones was discovered at the age of two years, when persistent pain in his left thigh after a fall led to x-ray examination. Until then his development, mental and physical, appeared to be quite normal, except that he was unsteady on his feet and had a mild degree of simple hypochromic anaemia. He has passed through various illnesses (measles, chicken-



FIG. 3.—Patient on August 13, 1935.



FIG. 4.—Patient on July 17, 1937.

pox, mastoiditis), has had numerous fractures and has developed disabling deformities. The entire osseous system has been involved. The changes in the bones have not been strictly symmetrical and those of the left side have been in advance of those of the right side. In the case of a fracture, healing has taken place at a normal rate. He has been remarkably free from pain even when a fracture has occurred.

CONDITION IN OCTOBER, 1938 : He was then ten years old. There was marked deformity of the whole skeleton (fig. 1-4). He had a marked kyphosis and anterior bowing of the sternum. The lower limbs were grossly deformed and unable to support him. His head was larger than normal and was increasing ; a year before the circumference was 23 in. and in October, 1938, 24 in., the antero-posterior measurement was 15 in. and in October 15½ in., the inter-meatal measurement was 13 in. and in October 14½ in. The veins of the forehead and face had become prominent. The original pigmentation had not altered appreciably. He was quite normal mentally, but it had been noted during the past two years that he was somewhat deaf. This may, of course, be due to his early mastoiditis, but as it has appeared comparatively recently, it is more probably due to pressure on the auditory nerve by the deformed skull bones. There was no evidence of otosclerosis (F. D. Marsh). Optic atrophy was also present, and as it was of recent development it might be due likewise to pressure on the optic nerves at the optic foramina. It is true, however, that optic atrophy is found in some cases of icterus gravis in whom there are no bone changes, but in them it is associated with other lesions of the central nervous system, the so-called kernikterus. In this case no other sign of lesion of the central nervous system has been found. Other organs were apparently normal, but the pulse rate was rather high, 90-120 per minute.

Laboratory investigations.—For convenience these will be described under three headings : (1) those concerned with mineral metabolism ; (2) those concerned with liver function ; (3) any other relevant investigations.

(1) THOSE CONCERNED WITH MINERAL METABOLISM.—The calcium, phosphorus and phosphatase of the blood serum have been estimated frequently over a number of years. The calcium has ranged from 8.4 mgm. per cent. to 11.2 mgm. per cent., and the phosphorus from 1.7 mgm. per cent. to 4.9 mgm. per cent. In view of the possible presence of liver cirrhosis the influence of liver extract on the ratio of calcium to phosphorus was observed. Campolon was given intramuscularly in 2 c.c. doses on alternate days for periods of two weeks, but no constant alteration was obtained. Liver extract given orally made no constant difference. Nor was any improvement in the x-ray appearance of the bones obtained after many weeks. The phosphatase has risen gradually but steadily, and has reached the high figure of 171 (mgm. of phosphorus liberated by 100 c.c. of serum when incubated at 37° C. for three hours).

TABLE I
CALCIUM, PHOSPHORUS AND PHOSPHATASE OF THE BLOOD SERUM

	AVERAGE VALUE	MONTH											
		iv	ix	iv	xii	xi	i	iv	viii	ix	iii	iii	ix
		YEAR											
		1931	1931	1932	1932	1933	1934	1934	1935	1935	1936	1936	1937
Ca : mgm. per cent.	10	9.8	10.56	8.97	10.8	11.2	10.14	11	9.2	10.5	10.4	9.6	1.04
P : mgm. per cent.	5	—	4.92	4.95	3.21	2.6	4.29	1.7	3.4	3.4	3.1	3.5	3.0
Phosphatase ..	6-10	43	—	16	—	—	—	—	134	152	162	171	153

Calcium and phosphorus metabolism experiments were made in 1931 over a period of three days, in 1932 over a period of five days and in 1937 over a period of five days on both a low and a high calcium diet. On each occasion there was a positive balance and at no time has there been any evidence of high urinary excretion of calcium (table 2).

TABLE 2
CALCIUM AND PHOSPHORUS METABOLISM
DAILY AVERAGE IN GRAMMES

DATE		INTAKE	OUTPUT			BALANCE
			STOOL	URINE	TOTAL	
April, 1931, 3 days	Ca	1.1788	0.373	0.011	0.384	+0.7948
	P	0.9641	0.1406	0.3340	0.4746	+0.4895
December, 1932, 5 days	Ca	1.017	—	—	0.644	+0.373
	P	1.024	—	—	0.063	+0.961
October, 1937, 5 days November, 1937	Ca only	0.184	0.094	0.004	0.098	+0.086
	Ca only	1.469	0.878	0.009	0.887	+0.582

Sulphur metabolism has been examined on one occasion. On a well-balanced diet of 1500 calories the daily average intake of sulphur over a period of five days was 819 mgm. ; the corresponding faecal output was 257 mgm. and the urinary output was 451 mgm.—that is, a total output of 708 mgm., or a total retention of 12 per cent. of the intake of sulphur.

(2) THOSE CONCERNED WITH LIVER FUNCTION.—It is a fact that cirrhosis of the liver may develop in affected children who survive. Pfannenstiel (1908) describes changes suggesting an early biliary cirrhosis in an infant who died on the twenty-first day ; Hawksley and Lightwood (1934) found signs of hepatic cirrhosis in seven out of nine patients who lived for more than five weeks ; and Braid and Ebbs (1937) found an advanced atrophic cirrhosis in one who died at the age of three and a half years. It seems worth while, therefore, to attempt to estimate the function of the liver in surviving children. This is admittedly difficult, but in dealing with an organ so complex in its functions even one positive result is of considerable significance.

(a) Protein metabolism : In the opinion of Mann and Bollmann (1926) tests concerned with protein metabolism offer a hopeful means of detecting liver dysfunction. They found that the function most easily impaired in dogs is that concerned with the destruction of uric acid, and that the amount of uric acid excreted in the urine was increased in direct proportion to the amount of liver removed. They consider that this may be of use in testing liver function in man. The blood uric acid and the output of uric acid have therefore been observed in this case. The fasting level of the uric acid in the blood was found to be high—6.1 mgm. per cent. as compared with an average normal of 3 mgm. per cent. On an ordinary diet (November, 1937) there was an output of 354 mgm. of uric acid in the urine in twenty-four hours and after a meal rich in nucleoprotein (3 oz. of chicken and 3 oz. of pancreas) 431 mgm. uric acid were excreted in twenty-four hours. This test was repeated in October, 1938. The daily urinary output (average of three days) was 302 mgm. of uric acid on ordinary diet and the daily output (average of three days) after a meal rich in nucleoprotein was 321 mgm. In one control case, a child of similar age but suffering from arthritis of the hip, the corresponding figures were 373 mgm.

and 302 mgm. ; in a second control case, a child of similar age but suffering from asthma, the corresponding figures were 267 mgm. and 298 mgm.

The manufacture of urea by de-aminization of amino-acids is a function peculiar to the liver, and may be examined by estimation of the blood urea and amino-acid nitrogen. The effect of a high protein meal on the blood urea was observed on three occasions. In 1934 it rose from a fasting level of 22 mgm. per cent. to 24 mgm. per cent. in four hours after a meal of 4 oz. of chicken. Similarly, it rose from 22 mgm. per cent. to 38 mgm. per cent. in four-and-a-half hours in 1936 and in 1937 from 21 mgm. per cent. to 42 mgm. per cent. in three-and-a-half hours. In 1937 the amino-acid nitrogen was observed at the same time and was found to be high relative to the urea. This is probably of more significance than the actual level of the blood urea (table 3).

TABLE 3
BLOOD UREA AND AMINO-ACID NITROGEN AFTER A HIGH PROTEIN MEAL IN MGM. PER CENT.

	AVERAGE VALUE	PATIENT				
		FASTING	FASTING	1 HR.	2 HR.	3 HR.
Urea .. .	30	21	25	25	36	42
Amino-acid nitrogen .. .	6·0	7·8	7·1	7·1	7·5	8·1

These results are not without interest, but in estimating their significance the position at once arises that there are no comparable figures for the same tests applied to normal children. It appears that the blood uric acid in this case is definitely raised, as also the urinary excretion of uric acid, and there is a definite disturbance of the ratio between the urea nitrogen and the amino-acid nitrogen. These facts suggest that the liver is deficient in function concerned with protein metabolism.

Estimation of the blood proteins has shown that the albumin and fibrinogen are normal, whilst the globulin is low. The total protein is low and is becoming gradually lower. The Takata-Ara reaction was positive at one time, but at the last estimation in 1937 was negative.

TABLE 4
BLOOD (PLASMA) PROTEINS IN GRAMMES PER CENT.

		ALBUMIN	GLOBULIN	FIBRINOGEN	TOTAL PROTEIN
1931		—	—	—	5·96
1934		—	—	—	5·87
1935	3·80	1·57	0·50	5·87	
1938	3·33	1·82	0·52	5·67	
Normal	3·8-4	2·5-2·6	0·15-0·6	6·5-7	

(b) Fat metabolism : Mann and Bollmann did not observe any demonstrable changes in the cholesterol of the blood following total removal of the liver. On the other hand, in the Annual Review of Biochemistry (1937) it is

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stated that a drop in the ratio of ester to total cholesterol in the plasma appears to be a prominent feature of liver injury. In the normal adult this figure varies from 2 : 3 to 3 : 1. Figures for children are not available. The blood fat has been analysed on two occasions and the results obtained are recorded in mgm. per cent. (table 5).

The normal total cholesterol is of importance in considering the differentiation from xanthomatosis generalisata ossium, in which condition it is usually high.

TABLE 5
ANALYSIS OF BLOOD FAT IN MGM. PER CENT.

	NOV. 1937	OCT. 1938	NORMAL ADULT
Total fatty acids	—	300	353
Total cholesterol	147	147	162
Phospholipoids	125	211	196
Free cholesterol	46.3	26	47
Combined cholesterol	—	121	115
Neutral fat	396	82	154

Fat balance was estimated in 1932 over a period of five days. The average daily intake was 45.8 grammes and the average daily output was 2.15 grammes.

Faecal fat analysis shows that there is no defect of fat digestion or absorption (table 6).

TABLE 6
ANALYSIS OF FAECAL FAT

DATE	DIET	PERCENTAGE FAT OF DRIED FAECES					EXCRETION PER DAY IN GRAMMES
		TOTAL	UNsap.	SAP.	FREE FATTY ACIDS	NEUTRAL	
4/31 : average	Almata and milk	39.1	16.1	23	3.8	12.3	1.8
5/31 : average	Ordinary diet	29.1	15.2	13.9	11.8	3.4	1.2
4/32 : average	"	25.2	10.6	14.7	7.4	3.2	2.4
12/32 : average	"	24.7	7.1	17.6	5.5	1.6	2.15
11/37	"	19.1	8.7	10.4	3.2	5.5	1.51
NORMAL	"	20-25	—	15	5	2	2

(c) Carbohydrate metabolism has been examined at various times and there appears to be an impaired utilization of sugar such as is observed in cases of liver disorder. The results obtained by oral test are not constant, indicating probably some irregularity in absorption (table 7).

TABLE 7
ORAL SUGAR TEST
(BLOOD SUGAR IN MGM. PER CENT.)

DATE	FASTING LEVEL	30 GRAMMES	MINUTES AFTER ADMINISTRATION						
			20	30	40	60	90	120	150
25/11/33 ..	69	Laevulose	—	72	—	72	116	79	67
26/11/37 ..	96	Laevulose	115	115	115	111	94	90	94
24/9/37 ..	87	Glucose	115	—	152	148	130	118	106
17/10/38 ..	90	Glucose	132	—	200	114	120	80	96

The intra-venous glucose tolerance test was carried out in 1935, but owing to a misunderstanding it was done during a period when campolon was being given and the results obtained were thereby confused. In 1937 and in 1938 this test was carried out under normal conditions and a delay in the fall of the blood sugar was shown (table 8).

TABLE 8
BLOOD SUGAR IN MGM. PER CENT. AFTER INTRAVENOUS DOSE OF
10 GRAMMES GLUCOSE

TIME (MINUTES)	NORMAL	PATIENT	
		2/9/37	11/10/38
Fasting	90	87	101
2	260	213	256
4	250	206	234
6	227	200	213
8	203	174	189
10	183	163	173
15	156	151	156
20	132	143	150
30	111	125	142
40	97	110	130
50	88	87	116
60	90	78	99

(d) Excretory function.—A high level of serum phosphatase is a feature of generalized disorder of bone, but it is also a feature of liver disorders. It has been shown by Armstrong, King and Harris (1934) that in experimental obstructive jaundice the serum phosphatase rose progressively; when the obstruction was relieved the recovery was accompanied by a fall in the phosphatase to its initial value. Roberts (1933) finds that there is an increased activity in the obstructive type of jaundice. Herbert (1935) confirms this and states that the phosphatase level bears no constant ratio to the degree of jaundice. Other workers have made similar investigations and observations, but an explanation of the findings is still wanting. Armstrong and Banting (1935) in considering the function of the phosphatase in the serum suggest that it is being carried there for the purpose of being excreted through the liver. The unusually high figures

in this case, along with the other evidence of liver failure, tend to support that suggestion and to indicate a failure of the excretory function of the liver. The high serum phosphatase related to the bone dystrophy has become excessively high because the normal excretion by the liver is not taking place.

(3) OTHER RELEVANT INVESTIGATIONS.—Blood vitamins, A, B, and C were estimated on 29.9.38 and were found to be below the normal level.

VITAMIN A	17.8 units per cent. (Clausen)—normal 20
VITAMIN B	3.9 mgm. per cent. pyruvic acid—normal 3.4
VITAMIN C	0.92 mgm. per cent. ascorbic acid—normal 1.25

The urine has contained an excess of urobilinogen since 1934. No Bence-Jones protein has been found and nothing to suggest any disease of the kidneys. The blood urea has always been at a low level.

The Wassermann reactions of the child and of his mother are negative.

The rabbit test for parathormone content of the blood has been carried out and no excess was found.

Blood analysis shows no abnormality of importance (table 9).

Biopsy. A piece of bone was removed from the shaft of the left tibia in December, 1938, and Professor Haswell Wilson has kindly supplied the following report.

No definite bony wall is recognizable, and this portion of the shaft of the tibia consists partly of hyaline cartilage and partly of coarse bony trabeculae. The cartilage is extremely cellular, with occasional small areas of calcification and on its inner aspect it merges into small spicules of imperfectly formed bone. The bony trabeculae are unevenly calcified and contain only occasional Haversian canals. There is no appearance of a lamellar structure, and canaliculi are scanty. Osteoblasts are present in small numbers at the periphery of the trabeculae, and there are occasional osteoclasts embedded in small depressions in the bone. The interstices between the trabeculae are completely filled by

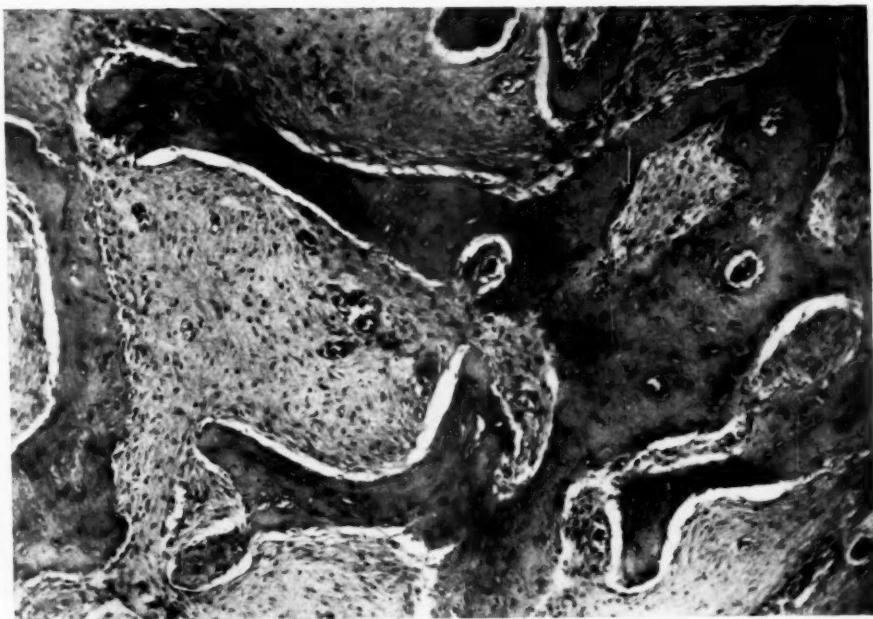


FIG. 5.—Case 1. Section of bone removed from left tibia (low power).



FIG. 6.—Case 1. X-ray appearances, October 2, 1930.



FIG. 7.—Case 1. X-ray appearances, November 7, 1933.



FIG. 8.—Case 1. X-ray appearances, November 7, 1933.



FIG. 9.—Case 1. X-ray appearances, October 27, 1938.

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TABLE 9
BLOOD ANALYSIS

	AUG. 1930	DEC. 1930	FEB. 1938	SEPT. 1938
Red blood cells, millions per c.mm.	3.755	4.320	4.470	4.670
Haemoglobin, per cent.	58	61	90	89
Colour index	0.77	0.7	1.01	0.96
Reticulocytes, per cent.	0.3	0.3	1.4	0.6
White blood cells, per c.mm.	7,550	—	8,700	12,900
Polymorphs, per cent.	—	—	28	43
Polymorphs (non-segmented), per cent.	—	—	16	18
Eosinophil (segmented), per cent.	—	—	1	3
Basophil, per cent.	—	—	2	2
Large lymphocytes, per cent.	—	—	31	18
Small lymphocytes, per cent.	—	—	8	7
Monocytes, per cent.	—	—	14	9
Films	—	—	Some anisocytosis	Normal

cellular and fairly vascular fibrous tissue, resembling that seen in osteitis fibrosa. There is no appearance of bone-marrow and the inner part of the specimen consists of hyaline cartilage of uneven consistence, with irregularly arranged cartilage cells and small areas of calcification. The line of junction between this cartilage and the bony trabeculae on the surface is extremely irregular, with a number of clefts and depressions filled by spongy-looking osteoid tissue (fig. 5).

X-ray report (Dr. C. G. Teall, October, 1938).—The radiographs at first showed increased diameter of the bones with thinning of the cortex, these changes

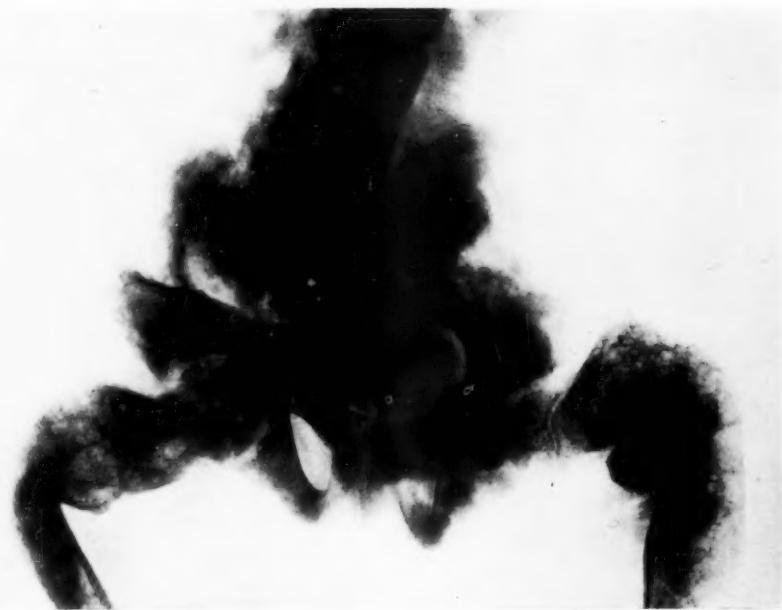


FIG. 10.—Case 1. X-ray appearances, October 27, 1938.

being shown chiefly in the femora. Later there was a cystic appearance at the ends of the diaphyses, a progressive increase in the diameter of the bones with

deformities and bending. Fractures appeared owing to the weakened bone structure. These changes became progressively more obvious as time went on, all the bones being affected more or less. The skull was not affected until late, but a similar type of change gradually appeared, until the whole bone structure became much expanded. The condition in the skull progressed in much the same way as it did in the long bones, until it was impossible to recognize any normal bone structure. The end result to date shows an extraordinary type of bone dyscrasia, in which the normal structure and architecture of the bones is completely lost. This is associated with marked deformities which have resulted from softening of the bones, and with fractures which have resulted from the mechanical weakness (fig. 6-13).

The only other bone dyscrasia of a similar type seen in the x-ray department of the Birmingham Children's Hospital has occurred this year in the case of I. D. (case 2, below). The bone changes (fig. 16-17) in this patient are similar in type and also progressive, but so far have not produced anything like the marked changes seen in the case of R. T. (case 1).

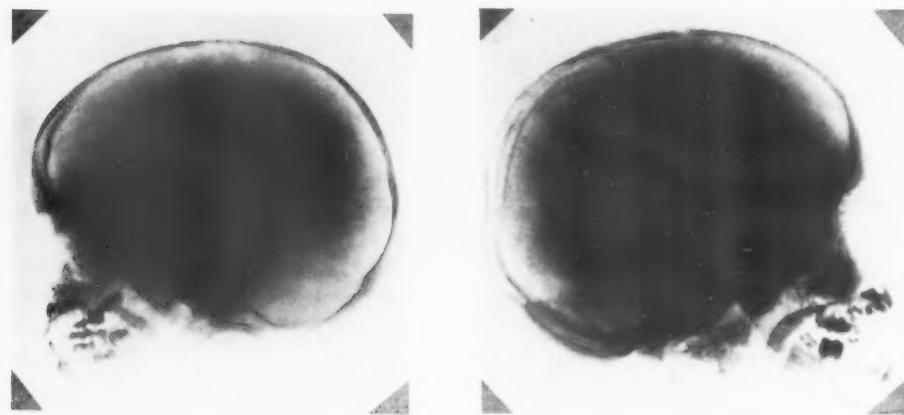


FIG. 11.—Case 1. X-ray appearances of skull, May 29, 1931.

FIG. 12.—Case 1. X-ray appearances of skull, November 24, 1937.



FIG. 13.—Case 1. X-ray appearances of skull, October 27, 1938.



FIG. 14.—Appearance in Case 2, 1938.



FIG. 15.—Appearance in Case 2, 1938.

Case 2.—I. D., female, the first child of healthy parents was born on September 6, 1936. She was jaundiced at birth and bled from the mouth, bowel, and umbilicus at the age of one week. Bleeding was arrested by 10 c.c. of horse serum, but the jaundice persisted and the stools were putty-coloured. When seen at the age of three weeks she was still jaundiced, had a slight degree of anaemia but was not wasted. The liver and spleen were not enlarged. An extensive pigmentation of the skin of the left side of the face, back of the head and right side of the back (fig. 14-15) was first noticed at the age of three months, and this has remained. At age of 1½ years the first of a series of fractures—left femur, right femur, left humerus, second left metatarsal—occurred and x-ray examination revealed the abnormal condition of all the long bones (fig. 16-17). Now she is small for her age but of healthy appearance, and her mental development is quite normal. There had been no evidence of precocious sexual development or other endocrine disorder until March, 1939 (age 2½ years), when enlargement of the breasts was noticed and she had a menstrual period which lasted for nine days.

Laboratory investigations.—These have been carried out on the same lines as in the first case, but owing to her age have been more restricted.

(1) THOSE CONCERNED WITH MINERAL METABOLISM.—The serum calcium has varied from 10.8 mgm. per cent. to 11.2 mgm. per cent. and the phosphorus from 2.1 mgm. per cent. to 3.8 mgm. per cent. The serum phosphatase is above normal, 16.2 units in April, 39.7 units in June, and 21.4 units in August, 1938. Calcium and phosphorus metabolism was examined on a diet of milk and Almata, and was found to be within normal limits (table 10).

(2) THOSE CONCERNED WITH LIVER FUNCTION : Plasma proteins have been examined in April and in September, 1938, and on each occasion have been

found to be normal. The average figures were albumin 3.44 grammes, globulin 2.47 grammes, and fibrinogen 0.71 grammes, total 6.62 grammes per cent.

TABLE 10
CALCIUM AND PHOSPHORUS METABOLISM
DAILY AVERAGE IN GRAMMES

DATE		INTAKE	OUTPUT			BALANCE
			STOOL	URINE	TOTAL	
May, 1938 (5 days)	Ca	1.00	0.975	0.013	0.988	+0.012
	P	0.99	0.483	0.121	0.604	+0.386

The fasting blood urea was 28 mgm. per cent. and the amino-acid nitrogen 5.5 mgm. per cent. The uric acid was 0.9 mgm. per cent. The cholesterol was 220 mgm. per cent. in April and 200 mgm. per cent. in September, 1938.

Analysis of the stools showed that fat digestion and absorption were normal (table 11).

TABLE 11
ANALYSIS OF STOOLS, AVERAGE OF 5 DAYS

Dried faeces	20 grammes.
Total fat	20.6 per cent. of dried faeces.
Unsaponified fat	17.1 per cent. of
Saponified fat	3.5 per cent. of
Free fatty acid	9.3 per cent. of
Neutral fat	7.8 per cent. of
Daily output	0.824 grammes fat.

The intravenous glucose tolerance test shows a normal curve. The urine contains an excess of urobilinogen and is otherwise normal. The van den Bergh reaction is negative.

(3) OTHER RELEVANT INVESTIGATIONS.—Blood vitamins have been estimated and all are low, as in the first case :

Vitamin A	13 units per cent. (Clausen)—normal 20
Vitamin B	3.8 mgm. per cent. pyruvic acid—normal 3.4
Vitamin C	0.83 mgm. per cent. ascorbic acid—normal 1.25

The Wassermann reaction is negative.

Blood analysis shows no abnormality of importance (table 12).



FIG. 16.—Case 2. X-ray appearances, September 1, 1938.



FIG. 17.—Case 2. X-ray appearances, September 1, 1938.

TABLE 12
BLOOD ANALYSIS

	28.9.36	2.10.36	5.4.38	12.5.38	24.9.38
Red blood cells, millions per c.mm.	4.05	4.3	5.57	6.8	5.29
Haemoglobin, per cent...	74	80	58	82	90
Colour index ...	0.92	0.96	0.52	0.60	0.86
Reticulocytes per cent. ...	—	—	1.7	1.8	0.6
White blood cells, per c.mm. ...	12,400	19,800	14,400	—	17,700
Polymorph neutrophils (segmented), per cent. ...	—	29	45	40	30.5
Polymorph neutrophils (non-segmented), per cent. ...	—	45	28	10	7.5
Basophils, per cent. ...	—	—	—	2	1
Eosinophils, per cent. ...	—	—	—	—	4
Large lymphocytes, per cent. ...	—	8	22	27	31
Small lymphocytes, per cent. ...	—	8	8	14	21.5
Monocytes, per cent. ...	—	10	7	7	4
Bleeding time ...	2-2 min.				
Coagulation time ...	2½-3 min.				
Film Hypochromia and anisocytosis			slight hypochromia	

Biopsy has not been done in this case.
The x-ray appearance of the bones is shown in fig. 16 and 17.

Comment

These two cases are alike in their history of neonatal jaundice of the icterus gravis type associated with acholia, in the presence of pathological pigmentation of the skin and in the fragility and x-ray appearance of their bones. To this extent they resemble the case recorded by McCune and Bruch (1937). In the older child there is evidence of some dysfunction of the liver and in the younger child the excess of urobilinogen in the urine is as much evidence as might be expected at her present age. They will therefore be discussed together ; they will be compared briefly with some known conditions characterized by a similar generalized disorder of bone and the possible explanation of its occurrence here will be offered.

In osteitis fibrosa cystica due to hyperparathyroidism the x-ray appearance is similar to that shown in these cases, and the serum phosphatase is high in the cases of hyperparathyroidism in which definite bone changes have developed. But the absence of hypercalcaemia and of hypercalcuria, the positive calcium balance, and the negative rabbit test for excess of parathormone in the blood in case 1 would appear to rule out that diagnosis. Absence of pain is unusual in hyperparathyroidism. Paget's disease has been considered. In a series of 154 patients suffering from Paget's disease the youngest was aged twenty-seven years and only thirty were under fifty years (Brailsford, 1938). Cases in children have been recorded, the disease being limited to one bone. In Hummel's (1934) two cases pathological pigmentation of the skin was present. Pain is a common feature of Paget's disease and is conspicuously absent in these cases. The affected bones support the individual in Paget's disease, but they do not do so here. The calcium metabolism is similar and likewise the high blood phosphatase. The sulphur metabolism does not correspond to that which, according to Rabinowitch (1932), differentiates Paget's disease from other generalized bone disorders. He claims that in osteitis deformans alone a negative balance is found. In his case there was a loss of 15 per cent. He quotes two cases in one of which there was a positive balance of 2.3 per cent. and in the other a negative balance of 43.8 per cent. In the older child the sulphur metabolism was estimated over a period of four days and found to show a retention of 12 per cent. of the intake of sulphur. The x-ray appearances are not unlike those reported by Fairbank (1927) as the cystic type of osteogenesis imperfecta. In that condition fractures heal slowly, as compared with the normal rate of healing in the cases now considered, and the serum phosphatase is not raised. Hansen (1934) found the serum phosphatase to be normal in four cases and at autopsy of one child aged seven years, it was normal in the blood serum, while in the periosteum and subperiosteal structure, where it is normally abundant, there was almost complete absence of phosphatase. Kay (1930) reported that the phosphatase was slightly increased in some cases, while Bodansky and Jaffe (1934) found it to be normal in six cases. Snapper and Parisel (1933) described a case of xanthomatosis generalisata ossium in a young girl who was mentally retarded and who showed evidence of precocious puberty. Hypercholesterolaemia is the usual feature in such a case and the lesions are not accompanied by marked swelling of the bones affected. The histological examination of the bone excludes that condition. The pigmentation of the skin raises the question of von Recklinghausen's disease, but the bone lesions in that condition are in the nature of subperiosteal or cortical cysts. It may be noted in passing that pigmentation of the skin has not been present in those cases of icterus gravis in which a bone lesion has not developed.

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Multiple cystic tuberculosis of the bones need hardly be considered, for there is no suggestion of tuberculosis in either case. Nor is there any evidence of renal disease, which might account for the changes in the bones.

The cases now recorded show important differences from those recognized conditions. But, as already mentioned, they do resemble unclassified cases which have been described recently in the American literature.

That described by McCune is of particular interest. The case is a female who in the first few days of life developed jaundice, the intensity and duration of which were such as to lead to a diagnosis of congenital atresia of the biliary ducts, a picture now recognized as one type of icterus gravis. The exact duration of the jaundice is not known. When the child was two years old, the parents became aware of numerous patches of pigmentation of the skin. At the age of one year bowing of the legs was first noticed and by the age of two years the deformity had so increased that locomotion became impossible. At the age of three years various osteotomies were done; healing took place promptly. At the age of three and a half years she sustained the first of a series of fractures. Another point of importance in her story is the evidence of precocious puberty. Menstruation began at two years and by the age of four years she was sexually mature. She also developed signs of hyperthyroidism at the early age of four, and by nine years the picture of hyperthyroidism was complete. Laboratory investigation showed that the blood calcium was 10.4 mgm. per cent. and the phosphorus 4.5 mgm. per cent. Calcium metabolism experiments on two occasions showed a positive balance, and there was never a high urinary calcium. The blood phosphatase was high. The neck was explored for parathyroid tumour, but none was found. The x-ray appearance, McCune says, was that of a diffuse and cyst-like osteoporosis sometimes accompanied by areas of sclerosis. The changes were considerably more advanced on the right side than on the left. He surveyed similar cases in the literature, excluded various etiological factors, but did not offer an explanation of the condition. Albright and his colleagues described seven cases, three male and four female, under the title 'syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty in the female.' In some of their cases exploratory operation had been carried out in search of a parathyroid tumour without success. Pigmentation was a constant feature and they suggested that its extent and situation bear some relation to the extent and situation of the bone lesion. Precocious puberty was a feature in all the females and in one male they thought there was a slight precocious bone development. In describing the x-ray appearance they said that the lesions tend to be unilateral; in almost all cases they are regional and tend to group themselves—e.g. in one digit or in one entire extremity; when the skull is involved there is less tendency to unilateral distribution. In discussing the nature of the bone lesion, they remarked that the distribution is not that of a metabolic disease. They thought that the amount of pigmentation varies roughly with the degree of involvement of the skeleton and bears some relation to the site of the bone lesion. In some, skin and bone lesions are confined to one side; in more, the bone lesions are predominant on one side, and in a few bone changes are extensive. This, they say, suggests an embryological or neurological disturbance. In the two cases now recorded the bone lesions happen to be extensive; in one case the pigmentation is not so extensive and is on the right side while the bone changes are somewhat greater on the left side. The precocious puberty and endocrine dysfunction in the females is difficult to explain. Albright suggests that as the gonad-stimulating hormones are known to be present in the anterior pituitary long before puberty, it may be that some releasing mechanism has

been brought into play and that it may be this releasing mechanism which is disturbed in the disease under consideration. He finds it impossible to accept a primary hormonal theory when the disease may be unilateral, and easier to believe 'that a hypothetical neurologic disturbance which causes the bone and pigment changes likewise initiates the endocrine disturbance.' The mental defect of one case adds weight to the theory that the condition is due to a widespread disorder of nervous tissue.

In looking for an explanation, the initial jaundice in the two cases now reported and in that of McCune cannot be ignored ; and the absence of mention of jaundice in Albright's cases does not exclude the possibility that it may have been present, for jaundice of the new-born from which an infant survived has hitherto been passed over frequently as a simple physiological jaundice and soon forgotten. The mental defect, details of which are not given, in one of his cases may indeed add weight to the theory that the whole condition is the result of a widespread disorder of the nervous tissue, but mental defect is also a well-known sequel to *icterus gravis neonatorum*. The distribution of the bone lesions in the present two cases does not render the theory of an etiological metabolic basis an unreasonable one to pursue, although the striking asymmetry in McCune's case and in some of Albright's cases does raise some doubt on this point ; yet the metabolic theory cannot be dismissed on that ground alone, for in renal rickets, for example, 'the changes in the bones are not seen to an equal extent throughout the long bones nor are they symmetrical' (Teall, 1934). An important sequel to *icterus gravis* is cirrhosis of the liver, and it may be that the etiological disorder of metabolism is the result of disordered function of the liver, evidence of which has been found in at least one of these cases ; there is both experimental and clinical evidence that a relationship does exist between liver disorder and bone dystrophy and between liver disorder and impaired use of vitamins, as shown in xerophthalmia.

Experimental evidence.—Buchbinder and Kern (1927) produced obstructive jaundice in puppies by ligaturing the common bile-duct. After sixty to seventy days there was 'a high grade rarefaction, cortical thinning with relatively wide open spaces, and a lack of contrast generally . . . one animal developed bilateral cysts in the bones.' They considered that the growth factor was important, for they found little or no change in adult dogs under similar conditions.

Greaves and Schmidt (1934) tested the action of viosterol in jaundiced rachitic rats in a series of well-controlled experiments. They gave viosterol orally and subcutaneously to rachitic rats in which the bile duct was ligated and divided, and also to rachitic rats in which laparotomy alone was performed. In the jaundiced rats it was found that viosterol was less potent than in non-jaundiced rats, whether given orally or subcutaneously, and they conclude that the jaundice was the cause of the diminished potency. They sought to show that this was not due to direct inactivation of the ergosterol by combination with bile acids, and this they did by administering orally and subcutaneously a mixture of viosterol and bile to non-jaundiced rachitic rats. In them the healing took place to the same degree as when viosterol alone was used. They considered that their experiments did not show that there is either diminished storage of vitamin D by the jaundiced liver or increased excretion by the jaundiced kidneys, and suggested that the failure of viosterol to aid calcification

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in jaundiced rats may be due to injury to or impaired function of the osteogenetic cells as a result of the jaundice. But they found no histological evidence of injury to these cells which might support this thesis.

Stimulated by the clinical observations of Gerstenberger (see below), Heymann (1938) conducted a series of experiments to study the anti-rachitic efficacy of vitamin D in rats in which cirrhosis of the liver had been induced by ligature and transection of the common bile duct or in which the liver had been damaged by carbon tetrachloride. Ten to twelve times as much vitamin D was needed to cure rickets in these rats as in rachitic rats in which cirrhosis had not been produced. To see if accumulation of bile in the tissues might have interfered with the calcifying property of osteogenetic cells 10 per cent. aqueous solution of sodium glycerophosphate was given intramuscularly. As calcification took place in the epiphyses of rachitic rats whether jaundiced or not, they concluded that the osteogenetic cells are not impaired in severe jaundice, as assumed by Greaves and Schmidt, and suggested that the diminished potency of vitamin D in rats with cirrhotic livers is the result of impairment of some particular function of the liver. They believe that their experiments confirm the clinical observations of Gerstenberger.

Clinical evidence.—Gerstenberger (1933) under the title 'hepatic rickets' described the occurrence of rickets in three children who also had cirrhosis of the liver. In two, aged about six months, this was secondary to congenital obliteration of the bile ducts, and in the third who was observed up to the age of twenty-seven months, the cause of the advanced cirrhosis found at autopsy was not known. These children developed rickets in spite of an adequate anti-rachitic diet and no improvement took place when treated with adequate doses of cod-liver oil or with the mercury vapour lamp. The blood phosphorus was low and the blood calcium was at a normal level. Fat absorption was about 50 per cent. in the two infants and in the older child between 80 and 90 per cent. He concluded that these children developed rickets which did not respond to the usual treatment because some function of the liver necessary for the use of irradiated ergosterol had been disturbed. Sneider and Weidmann (1935) in making observations on utilization of vitamins in Paget's disease came to the conclusion that there was some similar disturbance of the liver. An impaired utilization of vitamin A has also been noted. Wagner (1933) observed that children in whom there was some deficiency of liver function developed xerophthalmia more readily than did children in whom the liver was normal. Mellanby (1934) refers to a case of xerophthalmia in a man who had plenty of vitamin A in his diet but who had cirrhosis of the liver. He suggests that this may be due to 'non-functioning of the liver in preparing vitamin A to carry out its normal work.'

In the light of these experimental and clinical observations the results of investigation of liver function in the two cases now recorded deserve consideration in an attempt to explain the osseous dystrophy. In the two-year-old child an excess of urobilinogen in the urine is the only suggestion of liver defect which has yet been detected, and, taken by itself, is of limited significance. But more importance may be attached to it when taken in conjunction with the evidence of liver dysfunction in the ten-year-old child. In him an excess of urinary urobilinogen has been detected since he was six years of age ; the total blood protein was first noted at the age of two years, when it was lower than normal, and it has become progressively lower, the globulin being chiefly affected ; the ratio between urea and amino-acid nitrogen in the blood is upset, indicating a diminished capacity to manufacture urea ; the blood uric acid is

high and the urinary output is high, indicating a diminished capacity to destroy uric acid ; the glucose tolerance test shows an impaired capacity to utilize sugar. With these indications of liver dysfunction it is not unreasonable to presume that other functions which cannot at present be demonstrated are also impaired. It may well be that the function concerned with the storage and utilization of vitamins is impaired—indeed, the level of vitamins in the blood in both cases is lower than the average normal level—and the osseous dystrophy may be directly attributed to the liver dysfunction.

The female child began to menstruate at the age of two-and-a-half years. Such signs of endocrine disorder appear to be a constant feature in other female cases quoted from the literature. When they occur they may be due, as Albright suggests, to a disturbance of a releasing mechanism which normally controls the gonad-stimulating hormones in the anterior-pituitary. Does the liver exert any such control, and if so would dysfunction of the liver upset the normal mechanism of other endocrine organs ? Or, in view of the fact that a lesion of the central nervous system is known to occur in some surviving cases of icterus gravis, may not the endocrine disturbance be due to a central nervous lesion ? That does not explain why the endocrine disturbance is apparently sex-limited. Pigmentation of the skin is present in all cases noted, and the fact that it is not a feature of cases of icterus gravis who do not develop bone dystrophy is probably not without significance. This observation is merely recorded and no explanation attempted.

No solution of the problem can be complete until the etiology of icterus gravis itself is known, and that is still wrapped in obscurity. Whether one inclines to the belief that the disease is a primary abnormality of metabolism of the haematopoietic system, resulting in an outpouring into the blood stream of red cells which undergo rapid haemolysis, or to the belief that the erythroblastosis is secondary to a haemolysis resulting from some unknown toxin, the fact remains that an explanation for either an abnormality of the haematopoietic system or for the presence of a haemolytic toxin is still required. A toxin which might be responsible has not yet been found, in spite of many investigations. An abnormality of the haematopoietic system may be an inherited defect. The familial nature of the disease, the development of cirrhosis of the liver similar to that found in familial liver cirrhosis, and the occurrence of congenital malformations in some cases of icterus gravis suggest that the inheritance factor should be considered. In a recent study along this line Macklin (1937) concludes that 'icterus gravis is probably due to a dominant mutation occurring in the germ plasm of one of the parents. One does not find long pedigrees showing direct line of descent, for the disease usually ends in the death of the affected infant. . . . It recurs in the population only as the germ plasm of some person undergoes the appropriate mutation.' Some of the children who survive with present-day treatment may reach reproductive age and will thus support or confute the inheritance theory. Should it be ultimately proved that icterus gravis is due to an inherited defect then the question must arise whether what are now regarded as sequels to the disease may be merely associated congenital developmental defects.

Summary

- (1) Two cases are recorded with icterus gravis neonatorum, acholia, and a pathological pigmentation of the skin, and the same type of osseous dystrophy. The female shows precocious sexual development. Similar cases from the literature are quoted.
- (2) Report of biopsy of the bone in the older child is given.
- (3) Evidence of dysfunction of the liver is presented and the relation between liver dysfunction and bone dystrophy is discussed. Cirrhosis of the liver is a known sequel to icterus gravis neonatorum.
- (4) It is argued that in these cases the bone dystrophy is the result of failure of the liver to store and utilize vitamins and is therefore a sequel to icterus gravis neonatorum.
- (5) No explanation can be considered complete, however, until the problem of the etiology of icterus gravis itself has been solved.

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EPIPHYSEAL NECROSIS IN PITUITARY GIGANTISM

BY

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Drigalski and Diethelm (1937) recently described a case of gigantism, which showed degenerative changes in both hip joints. We have had an opportunity of observing a boy with similar symptoms, who is reported both on account of the rarity of these manifestations and in order to discuss the relation of the curious osseous changes to some bone diseases belonging to the group of epiphyseal necroses of bones (Aschoff, 1923). We hope to throw some light on the etiology of the above-mentioned disorder.

Case report

F. R., a boy aged six years, is the only child of healthy parents. The father and mother are of normal stature. According to the parents' statement, there are no known cases of abnormal height in the family. At birth the patient appeared to be unusually long, and his mother noticed the peculiar length of his toes. The child was exceedingly tall and broad when he began to walk at eighteen months of age. With the further development of the child, the parents noticed the rapid increase in size of his feet and especially of the toes, which frequently necessitated the purchase of new boots. The boy's growth greatly exceeded that of his contemporaries. For six weeks before admission to hospital the boy had complained of pains in his right hip and limped on the right leg. Walking was very painful. No other troubles were mentioned.

EXAMINATION on admission to the children's hospital at Brno on November 23, 1936, showed a tall boy of six years, who on account of his height looked considerably older (fig. 1). Height 53·9 inches (137 cm.) and weight 28·7 kgm. Average figures for his age, taken from Pirquet's and Kornfeld's examinations, are 45·2 inches (115 cm.) and 21 kgm. The shape of the head was mesencephalic. Innervation of the face was not abnormal. Mouth: mucous membranes and tonsils normal. Teeth well developed. Eyes: examination by Dr. Stein: on both sides the palpebral fissure was abnormally wide. Distribution of the scleral fields between temporal and nasal side is assymetric, which causes an apparent convergent strabismus. Both pupils are normally coloured, and surrounded by a ring of pigment. Vision 5/4. Range of vision normal.

The thyroid gland was not palpable. The internal organs showed nothing abnormal. The genitalia were well developed. Extremities: upper and lower extremities were extremely long, the length of the component parts being

increased distally. The length of both arms was 22 inches (56 cm.). Arachnodactyly (fig. 2) was present. The interphalangeal joints were slightly thickened. The fingers could not be passively extended, suggesting Dupuytren's contracture. The length of legs was 28.7 inches (73 cm.) from the anterior superior iliac spine to the left internal malleolus (right) and 28.9 inches (73.5 cm.) (left). Genu valgum was present. First toes were extremely long, the big toe on both sides measuring 2.3 inches (6 cm.), second toe 1.5 inches (4 cm.), third, fourth, and fifth toes 1.3 inches (3.5 cm.) (fig. 3).



FIG. 1.—The patient (right) besides a boy, aged six years of normal size (left).

The temperature remained normal throughout. The red blood cells numbered 5,200,000 per c.mm. and the haemoglobin content (Sahli) was 94.4 per cent. The white blood cells numbered 9,900 ; 2 per cent. were eosinophils, 1 per cent. were young forms, 2 per cent. were band forms, 58 per cent. were segmented, 30 per cent. were lymphocytes, 7 per cent. were monocytes. The sedimentation rate was three hours by Linzenmeire's microsedimeter. The urine was normal. The intracutaneous tuberculin test (Mantoux, 1 mgm.) gave a negative result. The basal metabolism was 51 per cent. below normal. Specific dynamic effect of proteins was after 60 minutes : 38.22 per cent., after 90 minutes : 79.21 per cent. (normally 20-40 per cent.) ; therefore 30 per cent. raised. The urine concentration was normal. The serum calcium content was

found to be 13 mgm. per 100 c.c. The blood sugar curve after oral administration of 50 grammes glucose was of normal type. Fasting blood sugar was



FIG. 2.—The hands show arachnodactyly. The deflected position of the fingers resembles Dupuytren's contracture.

100 mgm. per cent. After a quarter of an hour the blood sugar was 150 mgm. per 100 c.c., after half an hour it rose to 160 mgm. per 100 c.c., after an hour and a half the blood sugar fell to 75 mgm. per 100 c.c., after three hours and a

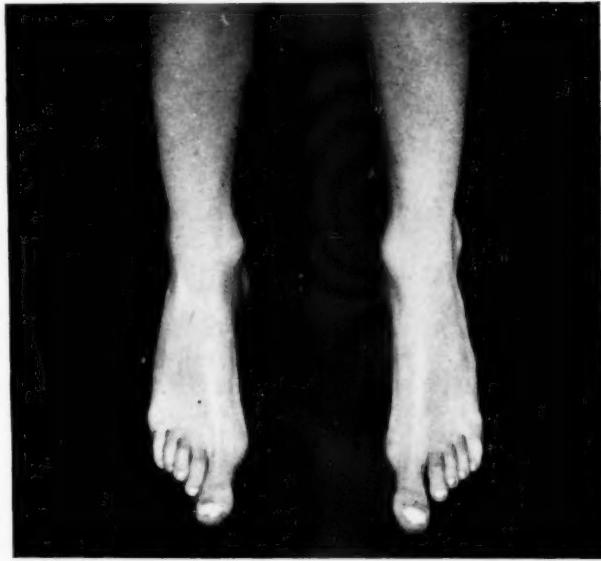


FIG. 3.—Photograph of the feet. First toes are extremely long.

half it regained its normal value of 100 mgm. per 100 c.c. (Crecelius-Seifert colorimetric method of determination).

The boy was apparently intelligent.

RADIOLOGICAL REPORTS (November 23, 1936) :
Hands : show arachnodactyly.

Feet (fig. 4) : 1. Navicular of tarsus on each side : The centre of ossification of the navicular is broken into several fragments the size of lentils. The particles have a heterogeneous structure and at some places the structure shows increased density.

2. First metatarsal on each side : The head of the first metatarsal is flattened, as though compressed, a little withdrawn and broken up into several fragments.



FIG. 4.—X-ray of feet (November 23, 1936). 1. Bilateral tarsal scaphoids are fragmented into pieces of irregular structure with areas of increased density. 2. The heads of first metatarsals are flattened and show some deep defects. The articular space is visibly and assymetrically enlarged.

The bone structure is in some places condensed. The articular space is visibly and assymetrically enlarged, the fibular side more than the tibial one.

Skull : No signs of increased intracranial pressure. The sella is normal.

Right hip joint : The right femoral head is flattened and shows irregularity of structure. The whole head is displaced, so that its cranial margin approaches the trochanter. The capital epiphysis shows a mottled appearance (*peau de léopard*). The neck is widened and shortened. The articular space is irregularly enlarged. The right acetabulum is flatter than on the left and shows an irregular outline (fig. 5).

Bodies of vertebrae (fig. 6) : The structure shows increased density (eburnization).

PROGRESS : On December 8, 1936, the right hip was fixed in plaster and on December 12, the patient was discharged. On account of the low basal metabolic rate, treatment with thyroid tablets was started. As the patient complained of being 'pinched,' the plaster was removed on January 21, 1937. On March 21, 1937, the patient was sent to the children's hospital at Brno for re-examination. The height of the child was 54·7 inches (139 cm.), the weight was 31·6 kgm. X-rays taken of his hips showed the following changes : The flattening and destruction of the capital epiphysis of the right femur was pro-



FIG. 5.—X-ray of hip joints (November 23, 1936). The right femoral head is flattened and displaced, so that its cranial margin approaches the trochanter. The epiphyseal plate shows a mottled appearance. The neck is shortened and widened.

gressing. The cranial margin of the head had reached the trochanter. X-rays of the feet : 1. The fragments of the ossification centres of both tarsal scaphoids had become larger. The disturbed relation between bone and cartilage seemed to have altered in favour of the bone. 2. Heads of the first metatarsals : The bony fragments had become larger. The flattening of the articular surface was decreasing. The articular space had become smaller (fig. 7).

A third examination of the boy in June 1937 showed a height of 55·5 inches (141 cm.). The patient visibly limped and complained of pains in the right hip joint.

An x-ray examination on November 22, 1937, showed in the right hip joint that the regressive process of the right femoral head was little changed. Feet : 1. The ossification of the navicular was progressing. The size of the scaphoid could distinctly be seen. 2. Head of the first metatarsal : Healing of the distal epiphysis was proceeding.

On June 17, 1938, a further examination of the boy (now aged eight years) showed his height to be 57·8 inches (147 cm.). The average figure for his age,

taken from Pirquet's and Kornfeld's estimations, is 50 inches (127 cm.). The length of bones : Anterior superior iliac spine to internal malleolus was 30.7 inches (78 cm.) on both sides. The length of the feet was 9.4 inches (24 cm.) (right) and 9.8 inches (25 cm.) (left).

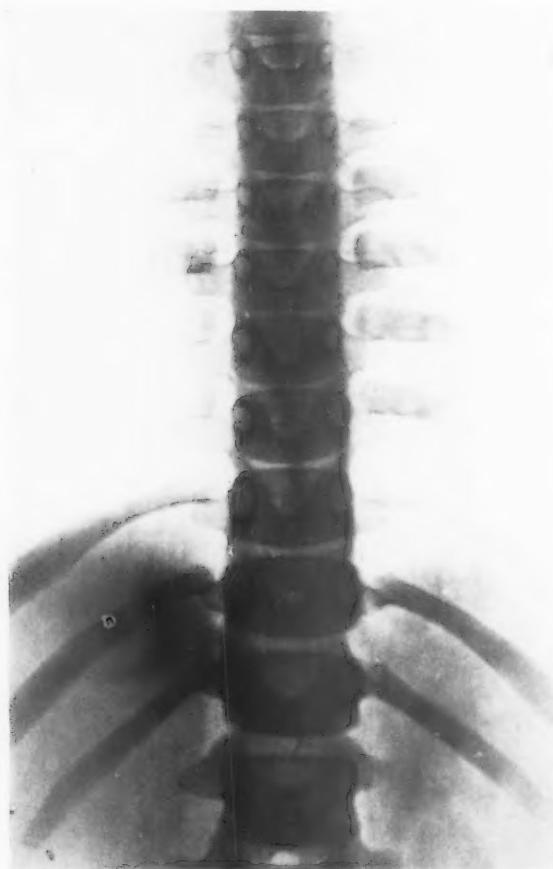


FIG. 6.—X-ray of vertebrae (November 23, 1936). Bodies of the vertebrae show increased density (eburnization).

RADIOLOGICAL REPORT :

Hip joints : The head, epiphysis and neck of the right femur were joined in a single mottled mass (fig. 8).

Feet : 1. The tarsal scaphoids showed irregularity of structure and increased density. The size and volume of the bone had become approximately normal.

2. First metatarsals : The heads of the metatarsals had regained normal size. In place of the former osseous fragments the bone was more calcified. The width of the articular space had become normal (fig. 9).

Bodies of vertebrae : The density of structure had become normal (fig. 10).

SUMMARY.—This is the case of a boy with pituitary gigantism. The low basal metabolic rate indicates a simultaneous deficiency of the function of the thyroid gland. A connexion between elevation of specific dynamic actions of protein (such as was observed in this case) and dysfunction of the pituitary body was formerly supposed, but has recently been questioned (Nobel, 1937). The patient exhibited arachnodactyly of the hands and feet. It has repeatedly



FIG. 7.—Feet. X-ray of feet (March 21, 1937). 1. The fragments of the centres of ossification of both tarsal scaphoids have become larger. 2. Heads of first metatarsals : The flattening of the joint plane is decreasing. The articular space has become smaller.



FIG. 8.—X-ray of hip joints (June 17, 1938). The right femoral head and neck are joined into a single mottled mass.

been suggested that arachnodactyly is associated with disturbance of the ductless glands. A deflected position of the fingers, as in the case of this patient, which resembled Dupuytren's contractures, has been observed in several cases of arachnodactyly. The x-ray examination of the boy revealed



FIG. 9.—X-ray of feet (June 17, 1938). 1. The tarsal scaphoids show irregularity of structure and increased density. The size of these bones has almost returned to normal. 2. First metatarsals : The heads are now of normal size and the irregular appearance has changed to more uniform ossification. The width of the articular space is normal.

osseous changes of the right hip joint, both tarsal scaphoids, the head of the first metatarsals and the bodies of the vertebrae.

Discussion

This case resembles Drigalski's and Diethelm's (1937) observation in so far as both patients showed pituitary gigantism accompanied by regressive osseous changes. Besides the disturbances of the hip joints, which according to the x-rays in both cases resembled osteochondritis deformans coxae juvenilis (Legg-Calvé-Perthes), the first patient showed changes in the tarsal scaphoids of each side, which could not be distinguished from the disease of the navicular described by Köhler. The heads of both first metatarsals also revealed changes,

like those which Köhler and Freiberg described in the heads of the second and third metatarsals. We have not found any report of a similar disorder of the first metatarsal in the literature. Finally there was eburnization of the bodies of the vertebrae.

There is the question if in the present and Drigalski's and Diethelm's (1937) cases the disorder of the hip joint could be interpreted as genuine Perthes' disease, and the changes in the tarsal scaphoids as Köhler's disease. Drigalski and Diethelm (1937) emphasize the fact that regressive osseous changes of the hip joint appearing in children with gigantism, and genuine osteochondritis



FIG. 10.—X-rays of vertebrae (June 17, 1938). Eburnization has disappeared.

deformans coxae must be strictly distinguished. The authors compare the above-mentioned changes in the bones accompanying gigantism with skeletal disorders in acromegaly, which, like gigantism, is caused by over-secretion of pituitary growth hormone. Brissaud (1931) and Erdheim (1930) conclude that the manifestation of gigantism or acromegaly depends on the age of the individual, and thus on the maturity of the epiphysis. If the excessive growth hormone meets open epiphyseal lines, it causes an increase of growth. Once endochondral ossification is completed, the growth hormone can no longer act in these areas. Regressive changes in bones and joints in acromegaly were described by Curschmann (1905), Fraenkel, Stadelmann and Benda (1901),

Dietrich (1909), Salus (1933), Steiger (1917), and Erdheim (1930). With these disorders Drigalski and Diethelm (1937) compare the changes in the head of the femur and vertebrae in their over-grown boy. They repeatedly emphasize that the condition observed by them only resembles Perthes' disease, though allowing that x-ray appearances similar to osteochondritis may be caused by different etiological factors. However, these authors wish to distinguish the osseous changes observed by them from genuine Perthes' disease.

It is assumed that regressive osseous changes in the hip joint accompanying gigantism cannot be convincingly distinguished from the condition generally known as osteochondritis deformans coxae juvenilis (Legg-Calvé-Perthes' disease). The x-rays of the present case show fragmentation of the right femoral head, which is flattened and displaced in the direction to the trochanter. The epiphyseal plate shows a mottled structure. The neck of the femur is thickened and shortened. The articular space appears wide. All these signs definitely resemble Perthes' (1924) classical description of x-rays of osteochondritis deformans. Several reports of Perthes-like osseous changes accompanying endocrine disturbances have appeared in the literature. Thus Erkes (1921), Riedel (1922), and Drehmann (1914) described cases of osteochondritis coxae occurring in adiposogenital dystrophy, Brandes (1920), Kostlivý (1922), and Roth (1918) mentioned Perthes' disease in hyperthyroidism, Benjamin and Miller (1938) in hypothyroidism, Läwen (1909) in cretinism, Dorner (1921) in pituitary dwarfism, Schmidt (1927) in gigantism.

The question if these osseous changes in the hip joints occurring in gigantism, such as are observed in the present case, should be interpreted as typical osteochondritis deformans coxae juvenilis, or as a bone disease sui generis, or as arthritis deformans acromegalica (Erdheim, 1930) can only be answered by a clear definition of the pathology of Perthes' disease.

It should be mentioned that there is no general agreement as to the pathology of osteochondritis deformans coxae juvenilis. There are authors such as Calot and Colleu (1922) who consider that the primary fault lies in maldevelopment of the acetabulum, which resembles the flattened acetabular cavity seen in congenital dislocation of the hip. The deformation of the femoral head is supposed to be a secondary change. In the same way Preiser (1907) regards the displacement of the articular surfaces accompanying malformations of the acetabulum as being responsible for the occurrence of osteochondritis. According to Köhler (1924) the disturbance of static unity in the hip joint (the dysarthria of Bibergel [1912]) is the reason for development of Perthes' disease, after bloodless reduction of congenital dislocation of the hip, after which a subluxation of the head of the femur often remains. The assumption that the trauma of reduction might be the reason for the epiphyseal necrosis is considered by Obadalek (personal communication) (chief of the orthopedic department of the children's hospital at Brno) to be contraindicated by the fact that changes in the head of the femur do not usually follow the reduction, but occur when the hip joint has to bear the weight of the body in walking and the disturbance of static unity comes into play. To these attempts to explain osteochondritis by functional activity, Perthes (1924) opposes the objection that the epiphyseal necrosis often occurs on the healthy side, and not in the hip in congenital dislocation. According to this author the displacement of the articular surfaces is not the cause, but the result of osteochondritis.

Perthes therefore agrees with the authors who consider the chief reason for

the occurrence of osteochondritis deformans coxae is an inherited disturbance of growth and ossification, occurring in the epiphysis of the head of the femur (Weil, 1921; Zaaijer, 1921; Fromme, 1920; Eden, 1912; Liek, 1922; and others). According to Perthes the inherited condition causes a loosening of the epiphyseal plate, due to which minor trauma may cause a laceration of blood vessels. As a result of these processes the typical changes of epiphyseal line may occur. Several authors consider that the disturbance of ossification may have a congenital basis, which is perhaps supported by the occurrence of hereditary cases of osteochondritis (Zaaijer, Weil, Perthes, Fromme and others). Another group of authors regard the underlying disorder as an endocrine disturbance (Liek, Sorrel, Benjamin-Miller, Sundt, Erkes, Läwen, Brandes and others). On this assumption of an endocrine cause of the osteochondritis, it is probable that abnormalities of osseous development would appear not only in the epiphysis of the femur, but also in other centres of ossification.

In any case, many authors regard the osteochondritis deformans coxae as part of a general skeletal disorder. There have been many reports on osseous changes occurring simultaneously with Perthes' disease. Fromme (1920) emphasizes that the osteochondritis is not a local disorder, but a symptom of a general disturbance of the endochondral ossification, and may therefore appear in each epiphysis. He mentions similar changes in the head of the second metatarsal. Since this note was published several cases have been recorded of osteochondritis coxae, occurring simultaneously with maldevelopment of other parts of the skeleton. Thus Weil observed absence of multangulum majus and minus. Perthes mentions large trochanters in several cases of osteochondritis coxae. Köhler describes two cases in which necroses of tarsal scaphoid (Köhler's disease) co-existed with osteochondritis coxae.

Similarly, in the case of the present patient, who was suffering from osteochondritis deformans of the right hip, the x-rays showed bilateral Köhler's disease of the navicular of the tarsus. Köhler considers that the co-existence of such disorders is much more frequent than the reports in the literature suggest. In only two out of a hundred cases of Köhler's disease, which Köhler found in the literature up to 1923, had the hips been examined. Otherwise, according to Köhler, this combination would be found more frequently.

Köhler's assumption seems probable. Like Fromme many authors have accepted his conception. In the same way, as Köhler, Freiberg and Fromme described analogous changes on the head of the second metatarsal, other reports have been published of changes in the tarsal scaphoid (Köhler's disease), Osgood-Schlatter's disease of the tibial tubercle, necrosis of lunatum (Kienböck's disease) and osteochondritis ischiopubica (first described by Van Neck, 1924), recently observed by Corper (1938). These osseous changes in different situations have been classified by several authors; Zaaijer (1921) uses the term osteochondropathia juvenilis parosteogenetica; Ombrédanne (1925): dyschondroplasia; Weil: dysplastic malacies; Aschoff: epiphyseal bone necroses. In this paper we have adopted Aschoff's nomenclature.

We consider that the same disturbance of ossification and growth as is caused by endogenous factors may be responsible for all the above-mentioned osseous changes. According to Weil all these disorders have a common characteristic, namely a displacement of the proportion between bone and cartilage in favour of the cartilage. Several symptoms are considered to be characteristic of all the conditions: The x-rays are similar, the disorder occurs mostly in boys, it appears during adolescence, it has a benign course, usually ending with complete recovery. In addition to the cases described by Weil, Perthes, Köhler, there is a report by Köhler of the association of Köhler's navicular disease with maldevelopment of the patella, whilst Sonntag (1922)

published a description of a child with Köhler's navicular disease, who showed a disturbance of the lower femoral epiphysis. Caan (1924) quotes Behn and Grashey who observed Köhler's disease associated with delayed carpal development, and Mandl's report of simultaneous appearance of Osgood-Schlatter's disease, slipped epiphysis of the trochanter, olecranon, calcaneus and tuberosity of the fifth metatarsal.

The present patient showed an unusual association of epiphyseal necroses. Besides a typical osteochondritis deformans of the right hip joint, there was Köhler's disease of both tarsal scaphoids. The spontaneous healing of the navicular disorder is significant ; this feature is, according to Perthes, characteristic of the epiphyseal necroses. The vertebral bodies showed eburnation. As a particular condition maybe mentioned the changes in the distal epiphyses of the first metatarsals. The peculiar x-ray appearance previously described in this case corresponds to the regressive osseous changes described by Köhler in the head of second and third metatarsals. The only difference in the present case was the absence of widening of the distal end of the metatarsal, which feature Köhler emphasizes, although he admits that there may be rare exceptions. Köhler doubts if Köhler-Freiberg's disease can occur in the first metatarsal. He maintains that all similar x-rays which he has seen have been examples of chronic arthritis. However, in the present case chronic arthritis can definitely be excluded, since not only are the articular spaces usually decreased in arthritis, but also the clinical course of arthritis is progressive, while in this case the cartilage of the metatarsal head showed an obvious tendency to heal. It is therefore concluded that the osseous changes in the head of the first metatarsal are subchondral necroses and classify this disorder in the group of epiphyseal necroses, which, as already mentioned, may occur in all parts of the skeleton. We have not found any report of epiphyseal necrosis of the first metatarsal in the literature.

The occurrence of multiple epiphyseal necroses in this case furnish strong evidence of disease affecting the entire skeletal system. It seems probable that this systemic disorder should be attributed to the endocrine disorder with which the patient was affected. Reliable authors, such as Köhler, Perthes, Zaaijer and others, maintain that the epiphyseal necroses must be caused by a disorder of the entire skeletal system. There are various opinions, however, as to the nature of the endogenous factor. Weil and Zaaijer believe that a congenital disturbance of development is responsible ; Fromme supposes late rickets ; Liek and others regard the cause as an endocrine disorder. In the present case the overgrowth might have caused a defect of the excessive cartilage and bony tissue produced. The view has already been mentioned that mechanical disturbances of the function of the hip joint may be responsible for the appearance of the osteochondritis deformans coxae. Similarly Köhler regards the abnormality of the tarsal scaphoid as due to the late ossification of the navicular of the tarsus, its defective blood supply, and the pressure exerted on it by the adjacent bones of the tarsus. The changes in the heads of the second and third metatarsals may, according to Köhler, be attributed to mechanical factors. He quotes Beely's observation that the foot chiefly rests upon the heel and the heads of second and third metatarsals, just the places where epiphyseal necroses are usually localized. It appears possible that in the present case the disorder of the tarsal scaphoid and the extreme length of the toes might have caused a displacement of the centre of gravity of the foot, so that the load

would fall not on the second and third but on the first metatarsophalangeal joint. This hypothesis might explain the appearance of regressive osseous changes in this unusual situation. The exceptional height of the patient may have caused a general disturbance of static proportions, resulting in the multiple epiphyseal necroses.

Summary

A case is reported showing multiple epiphyseal necroses, in which the whole skeletal system appeared to be affected. X-ray examination showed a typical osteochondritis deformans of the right hip joint : Köhler's disease of both tarsal scaphoids ; changes in the bodies of the vertebrae ; and epiphyseal necrosis in the heads of the first metatarsals, a condition which does not appear to have been reported previously. In many cases of epiphyseal necrosis nothing is known regarding the etiology of the osseous changes. In the case here reported, the skeletal changes appear to have been caused by endocrine dysfunction.

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DYSOSTOSIS MULTIPLEX : PFAUNDLER-HURLER SYNDROME REPORT OF TWO CASES

BY

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Pfaundler reported two cases to the Medical Society in Munich which were described in detail in 1919 by his assistant Hurler. They displayed the following unusual combination of congenital anomalies : clouding of the corneae, a deformity of the skull (oxycephaly), a disproportionate dwarfism strongly resembling that of hypothyroidism and associated with some of the usual signs of that condition (saddle nose, mental defect, dry skin, inguinal and umbilical herniae, crura valga, pedes valgi), a contraction of the fingers, limitation of movement in other joints (shoulders, elbows, knees) and defective hearing, to mention only the most striking features. Pfaundler at once suspected that he was dealing with a new syndrome. His assumption proved to be correct, as since his publication, twenty more cases have been recorded in Britain, America and Germany, showing the same combination of anomalies.

I recently had the opportunity of observing two similar cases in China. The publication of these seems to me to be justified, not only on account of their rarity, but also because the patients were brothers, because they are the first of their kind observed in China, and because they both presented in addition to the anomalies described by the other authors, a bilateral Sprengel's deformity (congenital elevation of the scapula) which was present, but overlooked in some of the previous cases. The name dysostosis multiplex was recently proposed for the syndrome. I consider it more suitable than the name gar-goylism, proposed by Ellis and his associates.

Case reports

History.—The mother is Chinese, and forty-five years of age. She has never been seriously ill. She had one miscarriage at the sixth month and six full-term pregnancies. Two of the children died from infectious diseases at the ages of ten and twenty-one years respectively. Two daughters, who have both been examined, are normally developed, anaemic, generally weak, but not otherwise abnormal. The father of the patients died from haemoptysis at the age of thirty-four. The maternal grandmother is sixty-four and had seven children ; one of them died two days after birth. The mother of the two patients here described was her second child. The third child died at the age of seven months, the fourth at the age of nine, the fifth at one year. The sixth child is alive and

healthy. The seventh child died at the age of sixteen years from heart disease. No deformities were noticed in the seven children nor in the ancestry. The paternal grandmother had six children, one of whom died from diabetes. The paternal grandfather died from syphilis. The present two patients were full-term children. The older will be called hereafter 'A', the younger one 'B.' During the fourth month of pregnancy of 'B' the mother took some Chinese drugs to induce abortion ; they caused haemorrhage. At birth 'A' and 'B' were of normal size ; each had an umbilical and bilateral scrotal hernia. The corneae of 'A' were clear; those of 'B' were cloudy. Both were breast fed. They only started walking and talking at the age of five years. The mother noticed in 'A' after one year, in 'B' after six months, that growth was retarded.



FIG. 1.

They seemed to her of normal size at birth. 'A' started to stand at the age of one year ; he could speak a few words, but his mental development subsequently stopped ; the mother thought this due to continuous intercurrent diseases (colds and coughs). 'A' always suffered from difficult, asthma-like respiration. 'B' suffered only from colds.

Examination of 'A'.—The patient was twelve years old; his growth was stunted, and he had the appearance of a malproportioned dwarf. His height was 1.155 metres on February 27, 1935. On April 14, 1935 (after thyroid therapy), and again on June 16, 1935, he measured 1.177 metres.

The expression of his face was idiotic ; the face was puffy and the lips thick. He spoke only a few words, and could not answer simple questions, but

he recognized people and was aware of his surroundings. He was of passive character. He did not attend school, and could not read or write. His gait was heavy.

The skin was dry and scaly, and covered with fine lanugo ; he frequently scratched himself. The skull was larger than normal and was out of proportion to the rest of the body ; its circumference was 54 cm., the occipito-frontal diameter was 18.3 cm., the biparietal diameter 14.5 cm. ; the occipital region was pointed, the forehead well arched ; the occiput fell abruptly from the vertex ; it was flat and ran parallel to the plane of the face. The fontanelles were closed ; the sutures could not be felt. The ears stood out abnormally and were rather low set. The root of the nose was flatter than that of a normal Chinese. There

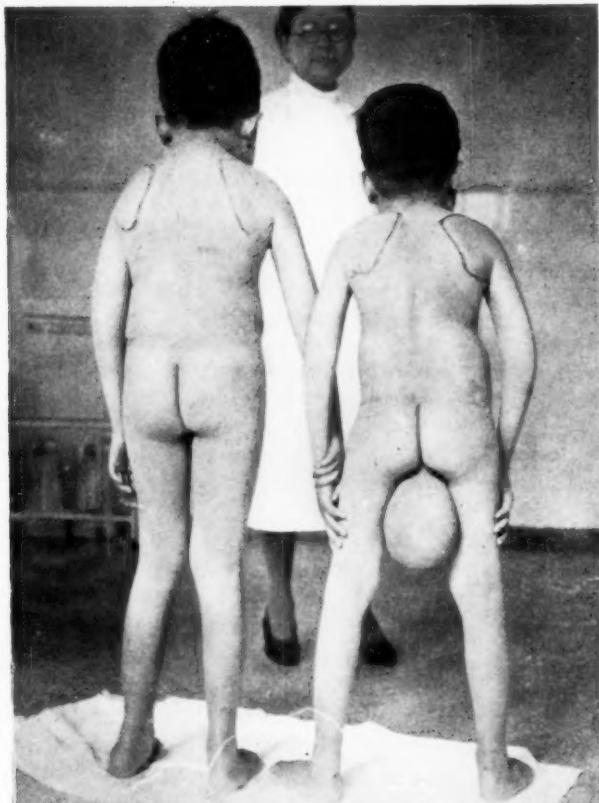


FIG. 2.-

was a constant dribbling of saliva from the open mouth ; the teeth were irregularly set, partly in two rows. There were twelve teeth in the maxilla and ten in the lower jaw. The jaws were massive. The right cheek was pushed forward by a tumour the size of a walnut which was localized in the horizontal part of the mandible, corresponding in position to the first molar tooth : it was bony hard, well defined, and felt like an exostosis of the mandible. The tonsils were large. The neck was short ; neither the thyroid nor the cervical lymphatic glands could be palpated.

The distribution of the subcutaneous fat in the body was normal, with possibly a slightly increased adiposity above and around the hips. The thorax was rather emphysematous ; no rosary of the ribs was palpable. Posteriorly,

there was a remarkable elevation of both scapulae, which were raised to the level of the upper margin of the shoulders. They were converging towards the head ; the inner border stood away from the thorax. The distance of the right angulus scapulae from the middle line was 6 cm., and that of the left 7 cm. The movements of both shoulder joints were considerably restricted ; active flexion and abduction of both arms was possible only up to the horizontal. During abduction the two shoulder blades stood out like wings, and the distance of the angulus from the mid-line was 10 cm. During forward elevation the angulus slipped as far as to the mid-axillary line (13 cm. from the middle line). The rotation in both shoulder joints was normal. No defect of any muscle could be detected either from configuration or function. The active movements of the body were normal. There was no deformity of the spine, and no cutis laxa. There was limitation of extension of both elbows of approximately 20°. There was clinodactyly of the fourth and fifth fingers (with convergence towards the radial side). The end of the fifth finger only reached the middle of the middle phalanx of the fourth finger. No obvious limitation of extension of the fingers was noticed, except that there was a tendency to hold the two thumbs in a flexed position.

A reducible umbilical hernia and bilateral indirect inguinal herniae were present ; all three were of the size of a man's fist. The penis was small and retracted into the hernial sac. The testicles were of the size of olives.

There was bilateral genu valgum of moderate degree, and limitation of extension of both knees, the maximal passive extension being 165°. This limitation was not due to the deformity of the knee.

The pulse was 96, regular and soft. The heart was enlarged towards the right side. There was a blowing systolic murmur in the mitral area. There were signs of bronchitis over both lungs. The abdomen was soft, with considerable divarication of the recti. The liver was enlarged, the upper border reaching the nipple line, the lower border being 5 cm. below the costal margin. The spleen was of normal size on percussion, and was not palpable.

OPHTHALMIC REPORT (Dr. Meyerbach).—Vision in both eyes approximately 0·2, binocular approximately 0·25. There was a diffuse dense clouding with turbid patches of both corneae strongly resembling keratitis parenchymatosa. The disc was pale on both sides, but not light enough to justify the diagnosis of optic atrophy. The pupillary reaction to light and accommodation was retarded ; one hour after application of homatropine they only dilated to a moderate degree and were normal.

The neurological findings were normal.

The urine was acid ; calcium oxalate was present ; there was no albumin and no sugar. The stool was normal.

Blood count : white blood cells 7,600 per c.mm., neutrophils 79 per cent., lymphocytes 16 per cent., mononuclears 5 per cent., eosinophils 0, basophils 0, no pathological forms. Haemoglobin 80 per cent.

Blood sugar : 130 mgm. per 100 c.c. blood. Chlorides : 511 mgm. per 100 c.c. blood.

Cerebrospinal fluid : clear, 5 cells per c.mm. Wassermann negative, Kahn negative, Nonne-Appelt negative, Pandy negative.

Basal metabolism : 16·3 per cent., at 37° C. temperature ; pulse 100 ; respiration 24.

For the purpose of testing the function of the hypophysis the water excretion was measured by Hoff's method under the following conditions : first without interference, secondly applying diathermy to the head (two poles bitemporal) for 15 minutes, immediately after the intake of fluid, and thirdly after an injection of pituisan. The result of the three experiments, carried out by Dr. F. Halpern on three successive days, showed that pituitary extract did not decrease,

and diathermy of the base of the skull did not increase, the diuresis, as it does under normal conditions. From this finding, dysfunction of the hypophysis was considered probable.

Water excretion of the kidneys :

8 A.M.	INTAKE	1000 C.C.	SPECIFIC GRAVITY
9 a.m.	output	180 c.c..	1000
10 a.m.	"	100 c.c.	
11 a.m.	"	250 c.c.	1001
12 noon	"	60 c.c.	1001
2 p.m.	"	40 c.c.	1010
4 p.m.	"	33 c.c.	1013
	Total	660 c.c.	

Examination of 'B'.—The patient was nine years old and was much smaller than the average child of his age. He resembled his older brother in every respect, so much so that I shall emphasize the differences between the two to avoid repetition. His height was 1·072 metres on February 27, 1939. On March 14, 1935 (after thyroid therapy) it was 1·076 metres ; on June 16, 1935, it was 1·08 metres, and on October 30, 1935, 1·095 metres.

The expression of the child was similar to that of 'A' though he was a little more intelligent. He took more interest in his surroundings, spoke more coherently, and had a bigger vocabulary. He was more cheerful and happy than 'A' ; he looked around the room, enjoyed playing, understood jokes, but did not read or write. His smile was like the *risus sardonicus*. The face was puffy and the skin similar to that of 'A.' In general he was the alter ego of his older brother. The circumference of the head was 52·5 cm., the fronto-occipital diameter 17·5 cm., the bitemporal diameter 12·5 cm. The skull was a little tower shaped ; the two temples were protruding ; the fontanelles were closed ; no ridges or sutures were palpable. The bridge of the nose was flat. There were twelve teeth in the upper and ten in the lower jaw ; none were of Hutchinson type. The tumour described in 'A' was missing.

The neck was short ; the thyroid gland could not be palpated. The thorax was narrow and flat in the upper region, and wide and barrel-shaped in the lower. The spine was deformed : there was a dextroconvex dorsal, and a sinistroconvex lumbar scoliosis with considerable torsion. The scoliosis was of a fixed type. The two scapulae were highly placed (see x-ray picture) ; they stood away from the thorax and their lower angles were divergent. The length of the scapula was 11 cm. (in the sagittal line), the greatest width 12 cm. ; they were mobile, and no bony strings were palpable around them. Both active and passive movement in the shoulders was much restricted : the lateral elevation on the left side amounted to 70°, on the right side to 80° ; elevation in front was 80° on both sides. The distance of each angulus scapulae from the middle line was 7·5 cm. during frontal elevation, and 13·5 cm. during lateral elevation. There was no paralysis of the shoulder muscles ; the patient could be lifted up by the elbows with adducted arms. All the muscles were present and their function was normal.

The movements of the two elbows were restricted ; active and passive extension could only be effected to an angle of 175°. The two thumbs showed flexor contraction and otherwise were of the same shape as those of 'A' (see x-ray picture). The other fingers were also similar to those of 'A.' There was no sign of rickets in the bones.

The knees could only be extended to 160°. There was a marked degree of genua valga and pedes plano-valgi. An umbilical hernia the size of an apple, and a right indirect reducible inguinal hernia the size of a child's head, reaching nearly down to the knees, were present.

The temperature was normal; pulse 87, regular and feeble. There was nothing abnormal in the heart; in the lungs there were signs of a mild bronchitis. The liver and spleen were of normal size; considerable divarication of the recti was present.

The right angulus was at the level of the fifth rib, the left at the level of the seventh; both were laterally dislocated. The left clavicle was horizontal, the right directed upwards corresponding to the higher scapula. The humeri and the rest of the visible skeleton appeared normal.

LABORATORY INVESTIGATIONS

Urine: albumin 0, sugar 0.

Blood count: leucocytes 7,900 per c.mm., haemoglobin 80 per cent., neutrophils 44 per cent., lymphocytes 50 per cent., normoblasts 6 per cent.

The Wassermann reaction of the blood was negative.

Cerebrospinal fluid: clear, 18 cells per c.mm., Nonne-Appelt +++, Pandy +++, Wassermann +++, Kahn +.

Blood sugar: 131 mgm. per 100 c.c. blood.

Blood chloride: 478 mgm. per 100 c.c. blood.

The water excretion test of Hoff gave a similar result to that in case 'A.'

OPHTHALMIC REPORT.—Palpebral fissure—Right 25 mm., Left 25 mm.

Vertical diameter of the cornea—Right 11.5 mm., Left 11.5 mm.

Horizontal diameter of the cornea—Right 12 mm., Left 12 mm.

Radius—Right 9.1 mm., Left 9.1 mm.

Refraction—Right 37 dioptres, Left 37 dioptres.

There was a marked diffuse clouding of the cornea which made the pupils so dim that an examination of the fundi was impossible. The reaction of the pupils was sluggish; half an hour after homatropine application they were only semi-dilated.

Fig. 3 of patient 'A' shows the high position of the scapulae.

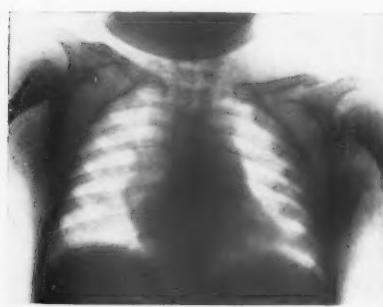


FIG. 3.

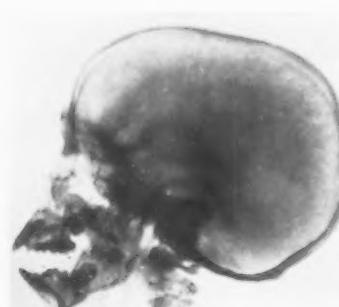


FIG. 4.

RADIOLOGICAL EXAMINATION.—Skull of 'A' (reported on by Mr. Norman Dott). Large slightly hydrocephalic type skull, a little thinner than the average. Thickness of vault remarkably even. Slight fullness in temples suggests increased pressure in later childhood (cf. oxycephaly). Sutures abnormally fused—even the coronal difficult to make out—yet sparse diploic venous channels clear enough. Frontal and mastoid cells practically absent. Sphenoidal cells absent. Sphenoid solid cancellous bone. Sella turcica small, rounded

cavity surmounted by short, thick dorsum sellae and indefinite decalcified posterior clinoid processes. Region of tuberculum sellae and anterior clinoids relatively low level, continuing straight back on level of olfactory plate instead of rising up ; also rather decalcified. 'Middle clinoid process' (completing carotid canal under anterior clinoid) ossified on one side. The whole picture suggests moderate hydrocephalus—not now actively progressive, and abnormal obliteration of suture lines.

Skull of 'B' : Similar features generally, but a younger skull ; it is not so



FIG. 5.



FIG. 6.

large and is less hydrocephalic ; suture lines of coronal and lambdoid visible though inconspicuous. Large, relatively symmetrical frontal diploic venous system. No sphenoidal air sinus. Floor of the anterior fossa continues back in low level, dipping gently into average-sized sella without any eminence of tuberculum sellae. Anterior clinoids are low set, not otherwise abnormal unless slightly decalcified. Dorsum sellae thick cancellous bone, average height. Poorly formed posterior clinoids (normal for age ?).

In addition to the retarded pneumatization of the sinuses, the extremely bulging temples and the unusually shaped massive, broad mandibular bone should be noted.

The x-ray pictures of 'A' and 'B' show no signs of rickets. The meta-



FIG. 7.

carpal bones are all present ; there is no retardation in their development. The terminal phalanx of both thumbs is in flexor position, the bones of both are cone shaped. The fifth finger of 'A' and the fourth and fifth fingers of 'B' show a strong inclination towards the radial side. The first phalangeal bones of 'B' are very large and clumsy. The middle phalanx of the fifth finger of 'A' is shortened, the diaphysis and epiphysis being nearly equal in length. Both hands show a certain webbing of the fingers.

To recapitulate briefly the findings in these two patients, the first point of interest is that they display a combination of exactly the same symptoms. The only difference between the two was that 'A' had a tumour-like swelling of the mandible, which was absent in 'B,' and that 'B' showed a scoliosis missing in 'A.' The cephalic signs were as follows : a deformity of the skull simulating oxycephaly, a massive broad jaw, delayed dentition, low-set ears, defective hearing, and congenital clouding of the cornea.

A second series of anomalies could be grouped under the heading endocrine disturbances, somewhat resembling myxoedema and consisting of dwarfism, diminished intelligence, broad saddle nose, dry puffy skin, congenital umbilical and congenital bilateral inguinal herniae, reduced basal metabolism, diminished water excretion, crura valga, and pedes plano-valgi.

The third group of signs concerns the osseous system (excluding the skull).

In both patients there was a bilateral elevation of the scapulae (Sprengel's deformity), restricted movement of the shoulder, elbow and knee joints, and flexion-contraction of the fingers with minor deformities of the phalanges.

Discussion

The following is a summary of the cases published hitherto and a discussion of the author's two cases in relation to the others. Since Pfaundler described two cases in 1919, twenty further cases have been recorded, the total number being now twenty-four. There is reason to assume that dysostosis multiplex is not as rare as this low figure suggests. Helmholtz and Harrington (1931) reported four cases and had knowledge of two others in the United States. Jewesbury and Spence (1927) observed one, Ellis and his associates (1936) seven cases in England, Putnam and Pelkan (1925) another case in U.S.A. Pfaundler's original two cases came from Germany, and mine come from China, a wide geographical distribution. In addition, single cases have been described by Liebenam, Binswanger and Ullrich, Slot, Ellis (1937, 1938) and Ashby et al.

Sex.—Out of twenty-four cases thirteen were boys, eleven girls. The two cases known to Helmholtz and Harrington were boys; both sexes seem to be equally affected.

Age.—All patients previously recorded were children between the second and seventh year, except one girl of eighteen years (Ellis), another of fifteen (Liebenam), and a boy of nineteen years (Ashby); the author's two cases were nine and twelve years old. A lowered resistance seems to prevent survival for long. The general inclination to colds is probably due to their narrow air passages. In the author's cases cardiac function was bad.

The syndrome is definitely hereditary, in spite of Hurler and Putnam, who claim otherwise. Of the twenty-four cases recorded the two cases of Helmholtz and Harrington were brothers, two were brother and sister and my two were brothers. A sister of the case I of Ellis had the same condition (case 2 Ashby). Jewesbury and Spence mention that a child of a paternal uncle had claw fingers, and resembled their case in appearance.

The deformities and anomalies are all congenital, that is to say that patients are born either with some anomalies or with the potentialities for their development. The signs and symptoms are discussed in three groups; first the anomalies of the head, second anomalies due to endocrine disturbances, third anomalies of the skeletal system apart from the skull.

Head.—The study of the skull in dysostosis multiplex is much less complete than that of such related conditions as oxycephaly. The reasons for this are that there have been only three post mortem records of dysostosis multiplex, and a thorough study of the skull in the living individual is bound to be incomplete and the majority of cases were in children in their first years when the skull is not yet definitely formed. The available reports and the x-ray pictures show that not one skull amongst the twenty-four was normal. They are described as scapho-, oxy-, trigono- and brachy-cephalic, and usually present

signs of early hydrocephalus, and a premature fusion of the sutures. The striking similarity between the oxycephalic skulls and those of dysostosis multiplex will be discussed later.

The sella is usually abnormal in size and shape, in some cases enlarged, in others small. In four cases of Ellis, in one case of Jewesbury and Spence, in one case of Helmholtz and Harrington and in two cases of Ashby and in that of Slot the sella was very elongated, but without evidence of bone erosion. The clinoid processes were often described as abnormal. In the autopsy of Hurler's case there was bowl formation of the sphenoid and the lamina cribrosa. In the middle fossa there were several bone defects of the size of a lentil, bridged by a fibrous membrane. There were exostoses on the base of the skull, but no sphenoidal sinus and no diploë present.

The signs of early hydrocephalus are of interest in the etiology of the condition ; they will be discussed elsewhere.

Clouding of the corneae was present in all the twenty-four cases, was congenital, and was usually so diffuse that it made examination of the fundi impossible. In some cases there were multiple punctate opacities, chiefly in the deeper layer of the cornea. The anomaly is considered in the literature to be due to an arrested development of the corneae. The author at first took its occurrence in his two cases for a syphilitic keratitis parenchymatosa, owing to the history of syphilis in the family and the positive Wassermann reaction in the cerebrospinal fluid in one of the brothers. But syphilis in China is so common that the post hoc ergo propter hoc is certainly not justified, especially as in all other cases there was no sign of syphilis. The Wassermann reaction was always negative. The blood Wassermann reaction of the mother in my two cases was negative, and there were no other signs of a syphilitic nature, either in the two patients or in their two sisters. Whilst the real nature of this anomaly is unknown, it is certainly not syphilitic.

In Helmholtz and Harrington's second case puffiness of the eyelids and narrowing of the palpebral fissure were noticed—signs to which the author attaches much significance. Internal strabismus was noticed in the case of Putnam and Pelkan.

In all cases where the ears were mentioned they were set very low, as may be seen in the picture of my two children. Defective hearing, also present in the author's two cases, is mentioned by Pfaundler and Helmholtz, and Liebenam and Binswanger. As a thorough examination of the ears was not obtained it is difficult to say whether the defective hearing was due to a retarded perception and slow reaction of unintelligent children or whether there was a real organic central or peripheral lesion. More stress should be laid on this point in future.

The tongue when mentioned in the reports was described as very large and often protruding from the mouth.

Endocrine disturbances.—Under this heading are summarized, rightly or wrongly, a group of signs which also occur in some known endocrine dysfunctions, although it may be said from the outset that they did not react to endocrine therapy. These signs are : (1) a characteristic facies ; (2) diminished intelligence and torpidity ; (3) dwarfism ; (4) dry pasty skin ; (5) con-

genital herniae ; (6) low basal metabolism ; (7) water retention ; (8) a dysfunction of the hypophysis in some cases with enlargement of the sella.

Concerning the facies, reference to the photograph (fig. 1) shows the similarity of the cases, a similarity so striking, that Pfaundler's first case, in spite of being a German child, resembles my Chinese children as much as if they were brothers. This striking resemblance, like that amongst acromegalic and cretinous individuals, is to be expected in an endocrine disturbance.

The intelligence was normal only in Liebenam's case. Helmholtz and Harrington described one case as mentally alert, but this statement about a child of seventeen months has to be accepted with reservation. All the other children were mentally retarded, more or less. There was difficulty in speaking, a symptom mentioned by nearly all authors, and torpor very similar to that of cretinism. The mental capacity did not improve on administration of thyroid in any case.

The dwarfism was disproportionate owing to the size of the head. The limbs were not strikingly out of proportion to the body. The shortness of the neck was due to the undescended scapulae. The degree of retardation of growth and the presence of hypogenitalism are difficult to judge, because only three patients reached adolescence. The retardation in growth was noticed in the author's cases at the age of six and twelve months respectively, a retardation attributed in other cases by the mothers to an intercurrent disease. Dwarfism was observed in twelve out of the twenty-four cases; in the others it was not noticeable, probably on account of the early age. It is significant that thyroid and pituitary extract medication did not influence growth appreciably. In the two females that reached puberty (Ellis and Liebenam) hypogenitalism was recorded with delayed menarche.

The dry, scaly skin, present in both the author's cases, is mentioned by Pfaundler and others. The puffiness of the face is described in several cases. Contrary to expectation in all the cases in which mention was made of the skin, a hypertrichosis was present : the body was covered, at least in parts, with a kind of lanugo, and the eyebrows were very well developed and dense, reaching to the mid line.

Large umbilical and bilateral inguinal herniae were present in both the author's cases, and a congenital inguinal hernia with or without a congenital umbilical hernia was recorded fifteen times out of twenty-four.

The basal metabolism and water excretion, not tested by the others, were considerably decreased in the author's cases ; Hoff's functional test of water excretion indicated a dysfunction of the hypothalamus or hypophysis.

The sella turcica has been described in detail ; and although it may appear at first sight to be enlarged, on account of the widening of the introitus to the sella and the flat enlargement of the sulcus chiasmatis, there is no indication of an enlarged hypophysis. The abnormal configuration of the base of the skull is rather the result of an early hydrocephalus. The hypophysis was normal at autopsy of Hurler's case, but much enlarged in Ashby's two cases..

All the symptoms just enumerated fit into the picture of a hypothyroidism, including dysfunction of the hypophysis, which is very often, though not always,

associated with hypothyroidism. Against the assumption of myxoedema are the normal ossification of the carpal bones (fig. 7), instead of retardation : the frequency of hypertrichosis, uncommon in myxoedema : and the failure of thyroid treatment to improve the mental state, promote growth or alter the facies and skin of the patients. There is no satisfactory explanation of these discrepancies. Ashby found on histological examination a foetal character of the parenchyma of the thyroid in one case and atrophy with secondary fibrosis in the other.

Osteoarticular anomalies.—There was great variation in the intensity and localization of the signs in the twenty-four cases under review. The upper extremities were usually more affected. The long bones had often a heavy square appearance. The pathological changes increased towards the distal ends. There was no evidence of rickets, except in two cases of Helmholtz. The fossa glenoidalis and the acetabulum were often described as shallow, the head of the femur and humerus as flat. A coxa valga was recorded twice by Ellis and once by Slot. The genua valga and pedes plano-valgi, present in the present two cases, were described also by several other authors. The case of Helmholtz displayed crura vara, one of Ellis' bilateral pes equinovarus, that of Slot a pes cavus, with an enlarged big toe. Minor deformities of the bones of the hand were present in several cases, and are to be seen also in fig. 7.

One of the most characteristic features is the restricted extension of the shoulders, elbows, fingers and knee joints. The most marked contractions were seen in the fingers ; described sometimes as 'claw fingers.' Flexion was always free. The limitation of the shoulder movements was due in my two cases, and in at least five others, to bilateral undescended scapulae.

Hurler noticed in one case a subluxation of the capitulum of the proximal phalanges towards the vola manus. The distal end of the radius and ulna were found irregular in the cases of Helmholtz and Slot. A broadening and thickening of the long bones are a common sign.

In one case mention is made of 'an unusual angulation of the collum humeri' by Hurler.

Deformity of the spine was present in all the cases recorded, except Putnam's, eighteen times in the form of a kyphosis, once (case 'B') as an S-scoliosis, twice as a kypho-scoliosis. Ellis and associates attribute the spinal deformities to a peculiar malformation of the vertebral bodies, which are irregular, flattened or wedge-shaped in outline, and may be considerably reduced in size. The vertebral body has often an anterior hook-like process. Ellis had an opportunity of comparing the radiological changes of the vertebral bones in Morquio's disease and in dysostosis multiplex, and says that 'too much emphasis cannot be placed on minor differences, unless these are found to be constant in a large number of cases, and at first sight one would be struck by the similarity rather than dissimilarity of the two types.' The peculiar wedge-shaped vertebrae are certainly of congenital nature, similarly to the deformities of the other bones. In my two cases there was no x-ray evidence of vertebral deformities. (No picture was, however, taken of the lumbar spine.)

One of the most conspicuous features of the present two cases was the

bilateral elevation of the scapulae (Sprengel's deformity). It is of interest not only because of the relative rarity of the bilateral form of this anomaly, but also because it supports the view as to the etiology of this intricate syndrome. Incidentally it indicates that a considerable number, if not all, cases of Sprengel's deformity are of hereditary origin, a view not yet generally recognized.

It is not surprising that the presence of this deformity has not been mentioned by any of the former authors, though its symptoms have been correctly described by some of them, and shown very conspicuously in a picture by Putnam, and the x-rays of Liebenam. A bilateral Sprengel escapes attention more readily than a unilateral one. If there are restrictions of other joints, the otherwise pathognomonic restriction of movement in the shoulders is easily misinterpreted as being in line with the contractions of the other joints (and dealt with summarily) and dismissed.

Hurler described in her first case the shoulder symptoms as follows : 'Die Hebung der Arme im Schultergelenk ist eingeschränkt. Heben gelingt nur bis zur Schulterhöhe durch starke Mitbewegung des Schulterblattes. Die Rotationsbewegungen bei fixierter Scapula nach vorn und rückwärts in geringem Umfang möglich'—a typical description of the symptoms met with in cases of Sprengel's deformity. The malformation of the scapula in her second case is also characteristic of the same disease. She says 'The substance of the shoulderblades appears very compact, the acromion much enlarged, the articular surface shallow and small.' Putnam says : 'The scapula, which appeared rather small and far apart, rotated strikingly as the arms were elevated, so that the outer borders and angles protruded several centimetres on each side of the body.' His picture is a typical example of an elevation of the scapula. In the x-ray of Liebenam's case the right scapula is at the level of the first, and the left scapula at the level of the second rib.

From these descriptions one can clearly recognize the presence of Sprengel's deformity in five cases. Helmholtz mentions in the history of case 1 that one maternal uncle of his patient had a large head and another 'a prominent shoulder girdle.' He mentions in two of his cases 'a short and thick neck,' also recorded by others, and in another, limitation of the shoulder movements. These signs may well have been due to elevation of the scapulae.

From this evidence it seems to be justifiable to include Sprengel's deformity as one sign of dysostosis multiplex. Elevation of the scapulae is rarely bilateral. Hayashi and Matsuoka collected from the literature up to 1912 only fifteen bilateral as against a hundred and ten unilateral cases. Out of the ninety-two cases collected by Horwitz, sixty-seven per cent. were associated with some other defect in another part of the body, a fact in line with experience of dysostosis multiplex, and pointing to its hereditary origin.

The discussion of the individual signs of dysostosis multiplex and their occurrence in the published cases shows that, in spite of their large number, there is a surprising constancy in their combination, with only minor variations in their degree. There is justification for considering the peculiar combination of these signs as a constant syndrome. How far this syndrome should be demarcated from others, will be discussed elsewhere.

Summary

Two cases of dysostosis multiplex of the Pfaundler-Hurler type (gargoylism), occurring in two Chinese brothers, are described in detail. In addition to the usual signs, both patients showed bilateral undescended scapulae (Sprengel's deformity), a sign that was present but overlooked in some of the cases previously described. It seems to be a part of the whole syndrome. The etiology will be discussed elsewhere.

Thanks are due to Mr. Norman Dott who kindly gave his expert opinion on the radiographs of my cases.

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MONOCYTIC LEUKAEMIA IN CHILDHOOD

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In 1913 Reschad and Schilling Torgau suggested the possibility of a distinctive hyperplasia affecting the monocytic cells of the blood under the name of 'splenocytic leukaemia.' With the more accurate title of 'monocytic leukaemia,' this is now an established entity. Though still regarded as a rare disease, this condition is being increasingly recognized. In 1933 only twenty histologically authenticated cases were on record (Gittins and Hawksley, 1933). By 1937 Osgood was able to review 133 cases, of which seventeen were children. The great increase in the number of cases recognized in the last few years suggests that the disease is commoner than at one time was thought likely, and later in this paper evidence will be brought forward to show how in many cases the diagnosis may easily be missed. Only a small proportion of recorded cases has occurred in children, yet here again increasing knowledge is bringing increased recognition. In 1936 Kato could only find records of five cases in childhood, yet at the Hospital for Sick Children five cases have been discovered in the last five years. The purpose of this communication is to consider the condition in childhood from the clinical, haematological and histological standpoints and to record two further cases.

Case reports

Case 1.—Male, aged five years. Pallor, the initial symptom, was first noticed in September, 1937. By February, 1938, this was more evident and in view of the development of a cough and excessive night sweats, he was admitted to the North Middlesex Hospital (February 14, 1938). Here the child developed what appeared to be measles, together with a very severe anaemia. One or two small bruises were present on both hands. The blood picture (February 22, 1938) is interesting :

RED BLOOD CELLS : 1,680,000 per c.mm.

HAEMOGLOBIN : 30 per cent.

COLOUR INDEX : 0.93.

WHITE BLOOD CELLS : 3,125 per c.mm.

POLYMORPHS : 43 per cent.

LYMPHOCYTES : 42 per cent.

MONOCYTES : 10 per cent.

PLATELETS : scanty.

Atypical and primitive lymphocytes and monocytes were recognized in the films, but they were regarded as being secondary to an aplasia affecting the bone marrow and resulting from toxæmia.

The child was treated by one transfusion of 200 c.c. blood, and campolon 2 c.c. and sodium pentnucleotide 10 c.c. daily for sixteen days. Following this an intermittent pyrexia, which had been present since admission, subsided and the general condition improved. At no time was there any clinical enlargement of the liver, spleen or superficial lymph nodes. The final blood picture was :

RED BLOOD CELLS : 4,370,000 per c.mm.

HAEMOGLOBIN : 72 per cent.

COLOUR INDEX : 0.8.

WHITE BLOOD CELLS : 9,300 per c.mm.

POLYMORPHS : 48 per cent.

EOSINOPHILS : 6 per cent.

LYMPHOCYTES : 38 per cent.

MONOCYTES : 12 per cent.

Improvement was maintained for a month. The child then began to lose weight, appetite and energy. The cough was still present, and in the middle of June he developed abdominal pain, always followed and relieved by defaecation.

On June 30, 1938, he was admitted to the Hospital for Sick Children.



FIG. 1.—Case 1 : Photograph to show marked enlargement of the cervical lymph nodes and the scars of old furuncles on buttocks and back.

EXAMINATION : A pale child of moderate physique. A purpuric rash with a few ecchymoses was present over both lower limbs and the right arm. There was no obvious bleeding from the mucous membranes. The buttocks showed numerous scarred areas, said to be the result of a series of furuncles which occurred during the previous illness. There was well-marked, generalized enlargement of the superficial lymph nodes, most obvious in both posterior triangles of the neck (see fig. 1). The tonsils were large, but otherwise appeared normal. The liver was enlarged three fingersbreadths and the spleen two fingersbreadths below the costal margin, the former being the more striking feature. Clinical examination of the chest was negative and a skiagram revealed a slight increase in the hilar shadows.

COURSE : The child was febrile on admission and intermittent pyrexia continued. Iron, campolon, sodium pentnucleotide and one blood transfusion were given, but the course was progressively downhill. For a few days before death there was considerable increase in the glandular swellings, gross haematuria and dysuria, and a severe ulcerative stomatitis. Death occurred on July 23, 1938.

BLOOD PICTURE : The initial blood picture, before the true nature of the condition was realized, was as follows :

February 7, 1938.—RED BLOOD CELLS : 2,760,000 per c.mm.

HAEMOGLOBIN : 44 per cent.

COLOUR INDEX : 0·8.

WHITE BLOOD CELLS : 19,700 per c.mm.

NEUTROPHIL POLYMORPHS : 1 per cent.

LYMPHOCYTES : 46 per cent.

MONONUCLEARS (nature doubtful) : 51 per cent.

PRIMITIVE CELLS : 2 per cent.

MEGALOBLASTS : 1 per cent.

ANISOCYTOSIS AND POIKILOCYTOSIS.

The diagnosis of monocytic leukaemia was made from the examination of subsequent blood films and confirmed by sternal marrow puncture and biopsy of a cervical gland. Supra-vital staining of the films proved that the majority of cells were monocytes. Those classed as 'atypical,' however, did not show the typical appearances of the monocytic cells (fig. 2).

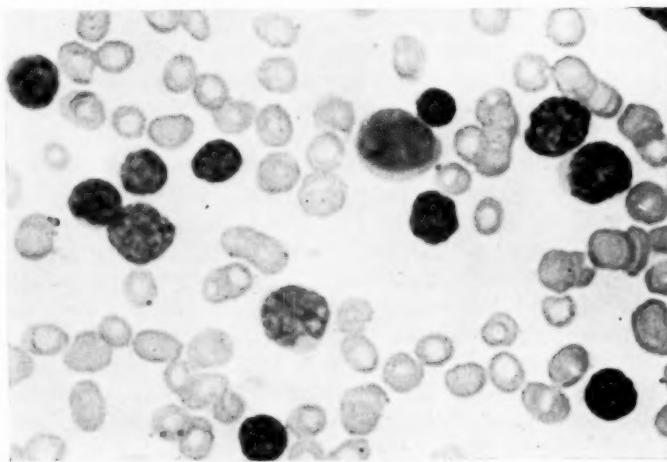


FIG. 2.—Case 1 : Leishman stain $\times 700$. Blood-film showing a monoblast with a lymphocyte beside it. There are several promonocytes and atypical cells ; two of the latter are at the bottom.

BLOOD-COUNTS

DATE	4.7.38	6.7.38	15.7.38	22.7.38
HAEMOGLOBIN, per cent.	45	—	46	18
RED BLOOD CELLS, in millions per c.mm.	3.46	—	—	1.14
COLOUR INDEX	0.65	—	—	0.78
WHITE BLOOD CELLS, per c.mm.	47,800	51,300	63,600	42,600
NEUTROPHIL POLYMORPHS, per cent.	0	0	9	0
METAMYELOCYTES (NEUTROPHIL), per cent.	0.5	0.5	0.5	0
MYELOCYTES (NEUTROPHIL), per cent.	0.5	0.5	0	0
LYMPHOCYTES, per cent.	11.0	18.0	13.0	5.5
MONOCYTES (MATURE), per cent.	0.5	0.5	8.5	0
PROMONOCYTES, per cent.	59.0	50.0	29.5	57.5
MONOBLASTS, per cent.	2.0	1.5	2.5	1.5
ATYPICAL CELLS, per cent.	26.5	29.0	37.0	35.5
NORMOBLASTS, per cent.	0	0.5	0	0
ERYTHROBLASTS, per cent.	0	0.5	0	0
MEGALOBLASTS, per cent.	1.0	0	0	0
PLATELETS, per c.mm.	46,000	—	—	41,000

SUPRA-VITAL STAINING (4.7.38)

	PER CENT.
MONOCYTES	54.5
LYMPHOCYTES	42.5
NEUTROPHIL POLYMORPHS	0
EOSINOPHIL POLYMORPHS	0.5
BASOPHIL POLYMORPHS	0
DOUBTFUL CELLS	2.5

STERNAL MARROW FILM (6.7.38)

	PER CENT.
POLYMORPHONUCLEAR	0
METAMYELOCYTES (NEUTROPHIL)	0.3
MYELOCYTES (NEUTROPHIL)	0.3
„ (EOSINOPHIL)	0.3
„ (BASOPHIL)	0.3
LYMPHOCYTES	7.3
MONOCYTES	0
PROMONOCYTES	52.0
MONOBLASTS	6.0
ERYTHROBLASTS	0.3
ATYPICAL CELLS	33.0

Histological report on the lymph node.—Cursory examination of a section through the node shows that the normal appearance has been lost, but with care a few follicles, some with secondary centres, together with the lymphatic sinuses and intervening medullary tissue, can be made out. Large masses of basophilic cells, which appear to be produced by proliferation in the medulla, are compressing the rest of the medulla, follicles and sinuses. These cells have a more or less uniform appearance. They are round or oval, have scanty basophilic agranular cytoplasm, and vary in diameter from 4μ to 8μ . Their nuclei, though varying in shape with round, indented or even convoluted forms, have a similar structure. The nuclear membrane is well marked, with condensation of chromatin at the periphery. There is a fine loose chromatin network, with nodes at the intersection of the chromatin threads and one or two nucleoli. A few cells are in mitosis. The cells are to be regarded as precursors of the monocytes of the blood (case 1, fig. 3). Amongst these masses of monocytic cells small sinuses can be made out, and there are in addition a few reticulum cells with pale-staining nuclei and indefinite outlines. There are many monocytic cells infiltrating the rest of the compressed medulla. Granular leucocytes are absent. The sinuses can easily be identified; some of the littoral cells are swollen, but they have not proliferated. There is no increase in fibrous tissue, nor in the argentophil reticulin fibres. Large numbers of monocytic cells are infiltrating the capsule and peri-capsular tissues.

Autopsy.—For religious reasons a complete examination was refused, but

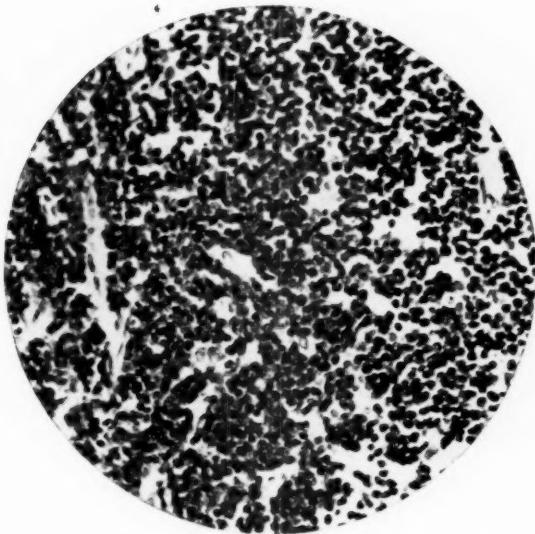


FIG. 3.—Case 1 : H. & E., $\times 240$. Section of lymph node to show infiltration of medulla by monocytic cells.

portions of liver, spleen and kidney were removed through a small abdominal incision. A segment of rib was also excised.

The body was that of a well-developed, moderately nourished child. There was marked pallor but no other external abnormality apart from the scars of old furuncles, already mentioned.

SPLEEN : Moderately enlarged. Weight 270 gm. Cut surface thick and fleshy, with no Malpighian bodies or localized deposits.

LIVER : This was greatly enlarged, pale and yellow on section, and with no apparent deposits.

KIDNEYS : Extremely pale and grey in colour. A moderate-sized area of haemorrhage was present in the upper pole of the left kidney and a smaller one in the lower pole.

Histological examination.—**LIVER :** Sections showed well-marked infiltration of the portal tracts with monocytic cells, similar to those seen in the biopsy of the lymph node ; there were in addition a few eosinophil leucocytes. There was a moderate degree of fatty infiltration of the hepatic cells, most marked at the centre of the lobules. Cells in the neighbourhood of the portal infiltrations were atrophied. The Kupffer cells showed evidence of phagocytosis of erythrocytes and monocytes, but were not increased in number, and there was no evidence of their conversion into free phagocytic cells. Free iron could be demonstrated in the hepatic and Kupffer cells but not in the monocytes.

SPLEEN : There was marked compression and atrophy of the follicles and an infiltration of the medulla with monocytic cells. Only a few granular leucocytes and myelocytes were seen. Monocytic cells were lying free in the sinuses. These appeared to have a more plentiful cytoplasm and some had the appearance of plasma cells. No free iron could be demonstrated by the Prussian blue reaction.

KIDNEY : The glomeruli were healthy, but the cells of the tubules showed fatty degeneration. Monocytic cells could be seen in the blood-vessels and there were, in addition, small areas of infiltration by these cells into the interstitial tissue, particularly in the neighbourhood of the arterioles (fig. 4). This proximity to the blood-vessels is of interest, as it suggests a local origin of monocytes from the undifferentiated mesenchymal cells to be found in the

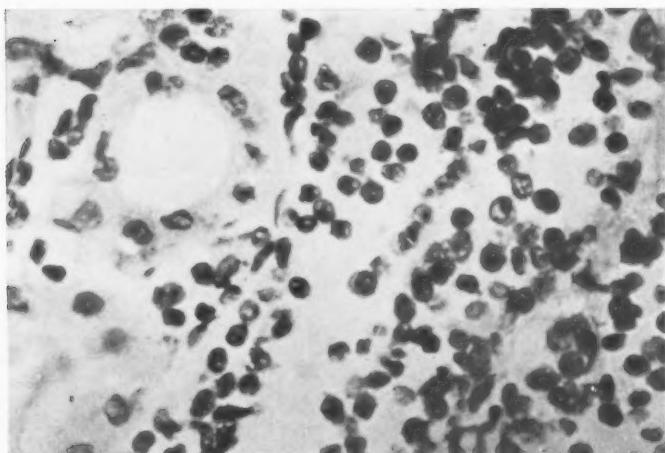


FIG. 4.—Case 1 : H. & E., $\times 550$. Section of kidney showing infiltration by monocytic cells.

adventitia of blood-vessels (cf. Robb-Smith, 1938). A similar paravascular distribution of the infiltration in the kidney was found by Hernandez (1938) in one of his cases.

RIB : The portion of rib was examined after decalcification. Infiltration by monocytic cells could be seen in the muscular and fatty tissue round the bone and also beneath the periosteum (fig. 5). The marrow was extremely



FIG. 5.—Case 1 : H. & E., $\times 40$. Section of rib. There is infiltration beneath the periosteum and also into the connective tissue outside the periosteum, which is shown on the left.

cellular and the majority of the cells were monocytic. Granular leucocytes, myelocytes, erythroblasts, normoblasts and megakaryocytes were present, but in a much reduced proportion from the normal. There were, in addition, a few cells with large oval nuclei and an indefinite cell-outline.

Case 2.—Female child, aged four and a half years. Admitted to the

Hospital for Sick Children on December 11, 1938. The child appeared well and happy until fourteen days before admission ; she then began to complain of severe headaches and epigastric pain on walking short distances. This was accompanied by nausea, anorexia and listlessness.

EXAMINATION : Well-built girl; pale and rather quiet. Mouth and tonsillar region normal. No bleeding from the gums. Spleen moderately enlarged. Liver just palpable. Small lymphatic glands felt in the right side of the neck and in the right axilla. These did not increase in size during the course of the illness. No purpuric spots seen anywhere, but a few bruises were present in the region of both knees. Moderate pyrexia 99° - 100° F.

A diagnosis of monocytic leukaemia was made from the blood and sternal marrow films. Small retinal haemorrhages were noticed during the terminal stages. Despite blood transfusion (250 c.c.) the child's condition deteriorated rapidly. Death occurred on December 23, 1938.

STERNAL MARROW PUNCTURE

STERILE MARROW PUNCTURE						PER CENT.
NEUTROPHIL POLYMORPHS	2·0
EOSINOPHIL POLYMORPHS	0·5
BASOPHIL POLYMORPHS	—
NEUTROPHIL METAMYEOCYTES	3·5
NEUTROPHIL MYELOCYTES	3·5
LYMPHOCYTES	29·0
MONOCYTES	4·0
PROMONOCYTES	33·5
MONOBLASTS	5·5
INDEFINITE	3·5
NORMOBLASTS	6·5
ERYTHROBLASTS	3·0
MEGALOBLASTS	5·5

BLOOD-COUNTS

Autopsy.—The body was that of a well-developed child. Weight 35 lb. ; height 3 ft. 10 in.

THE BRAIN was pale, but otherwise normal.

THE HEART weighed 105 gm. There was marked fatty change, with the production of the thrush-breast appearance under the ventricular endocardium.

THE LUNGS were pale and oedematous and there were a few sub-pleural haemorrhages.

THE LIVER was much enlarged and weighed 900 gm. It was of a general yellow colour and was mottled with small, glistening, orange-yellow areas.

THE SPLEEN was also greatly enlarged, weighing 265 gm. ; it was dark red in colour, but on section showed stippling with small irregularly shaped areas of whitish-grey, each surrounded by a red zone of haemorrhage.

THE LYMPH-NODES were not enlarged in any part of the body.

THE KIDNEYS were extremely pale and had an average weight of 80 gm. On section the cortex appeared yellow. There were several wedge-shaped infarcts.

THE ADRENALS were normal.

THE THYMUS was moderately enlarged and pale.

THE STOMACH and INTESTINAL TRACT displayed no abnormality.

Histological examination.—LIVER : In the liver there was well-marked periportal infiltration, the majority of the cells being identified as monocytes or monoblasts. Many, however, were smaller than the typical monocyte and had more darkly staining nuclei and thus resembled lymphocytes ; these cells were undoubtedly similar to those seen in the blood films and termed 'atypical.' There were in addition a few granular leucocytes and myelocytes. Many of the liver cells showed a moderate degree of fatty degeneration. The sinuses contained many monocytes ; the Kupffer cells were not especially prominent, but a few showed erythrophagocytosis.

SPLEEN : The lymph-follicles of the spleen were inconspicuous and had been compressed by a marked proliferation of cells in the pulp. These consisted almost entirely of typical and atypical monocytic cells, but there were a few granular leucocytes.

BONE-MARROW : Sections of the bone-marrow showed it to be cellular and to consist mainly of monocytes. There were only scanty numbers of granular leucocytes and myelocytes, megakaryocytes and nucleated precursors of the erythrocytes. There were, however, a few large histiocytes, some of which showed evidence of phagocytosis.

THYMUS : There had also been extensive infiltration of the original lymphoid tissue of the thymus with monocytic cells, but the differentiation of the two types of cells was made difficult by the presence of the 'atypical' lymphocyte-like cells.

HEART : The heart muscle showed no obvious abnormality apart from the blood-vessels containing large numbers of cells, due to the escape of many primitive forms into the circulation before death. Many of the cells were small and darkly staining, which agrees with the last blood-count. This showed that the majority of the cells, then beginning to flood the circulation after the preceding leucopenia, were of the 'atypical' variety.

THE LUNG showed oedema and large numbers of monocytes in the capillaries of the alveolar walls, as well as in the larger blood-vessels.

KIDNEY : Similarly in the kidney there were many monocytes in the capillaries, but no interstitial infiltration. The glomeruli were normal and the cells of the tubules showed post-mortem change only.

Discussion

An increasing number of cases of monocytic leukaemia is being recorded and analysis of their features has established a clinical picture for adults. No similar attempt has been made to define the condition in childhood. In Osgood's (1937) recent review, seventeen patients were children. Hernandez (1938) has described the clinical and histological findings in two other cases. Four further examples have occurred in this hospital; one has been reported previously (Newns and Signy, 1938, case 2), and full details of two others have been given here. A further case at this hospital, reported by Lightwood and Hawksley, is included in Osgood's collection. These twenty-three authentic cases will be analysed in this paper. The five cases from this hospital have occurred in the last five years. During this period, thirty-five children with leukaemia were admitted to the wards. Apart from the five examples of monocytic leukaemia, twenty-nine had lymphatic leukaemia and one probably myelocytic. Lymphatic leukaemia is therefore much the most common in childhood, and the twenty-nine cases mentioned above will serve for purposes of comparison in this communication.

The following clinical features will be considered.

AGE : The youngest case reported was eleven months. The average age was six years and three months. In the lymphatic series, the average age was four years and three months. Only 40 per cent. of the monocytic group were under five years of age, as compared with 64 per cent. of the lymphatic. This suggests that monocytic leukaemia tends to occur rather later in childhood than the other types. This may be contrasted with the traditional view that, in children, leukaemia as a whole tends to occur in the first four years of life (Whitby and Britton, 1937).

SEX : Males are more frequently attacked than females in the proportion of three to two. A similar ratio is found in adults.

DURATION : The average duration in the monocytic series was sixteen weeks; the longest period was twenty-one months and the shortest ten days. In the lymphatic group the average duration was ten weeks, with a maximum period of ten months and a minimum of ten days. In four of the monocytic cases the disease lasted for six months or over, and in three of these a definite remission, extending over a period of months, occurred. During this time the clinical condition reverted towards the normal and the anaemia responded to treatment. This is well exemplified in case 1. The blood monocytes remained persistently above the normal level and were qualitatively abnormal. Whitby and Britton (1937) emphasize that relapse in almost every case is preceded by an infection usually affecting the upper respiratory tract. Though in many cases the exact onset is difficult to determine, once established the disease usually runs a rapid course. At the same time sub-acute or remittent cases occur rather more frequently than in other leukaemias. These contrasting types are excellently illustrated by the two cases reported in this paper.

ORAL LESIONS : Lesions in the mouth occurred in 52 per cent. of the monocytic, as compared with 20 per cent. of the lymphatic series. These consist of soreness, bleeding from the gingivae, swelling and necrosis of the mucous mem-

brane, which may extend on to the tonsil or soft palate. Although these lesions give rise to some of the most striking symptoms in adults, in whom necrosis of the mucous membrane may reach the degree of a diffuse cellulitis, only the milder forms occur in childhood. In only two cases has necrosis been a prominent feature. In the first cases reported by Ernandez (1938) this was the presenting feature. But in the remainder simple bleeding and superficial ulceration alone were present, and in many cases it was then only a terminal feature. Although a suggestive symptom, the claim made by Forkner (1934) that this picture of diffuse and marked swelling of the mucous membranes, particularly affecting the gingivae, with ulceration and necrosis, is characteristic of monocytic leukaemia and is usually absent in the other forms of acute leukaemia, is not substantiated by a review of monocytic leukaemia in childhood.

HAEMORRHAGIC FEATURES : Purpura was noted in 76 per cent. of the monocytic and 67 per cent. of the lymphocytic series. In the former, petechiae, often widespread, were the usual manifestation ; in the latter, ecchymoses and larger areas of bruising were more in evidence. Retinal haemorrhages were frequent. In the terminal stages bleeding from any mucous surface occurred, notably haematemesis and haematuria. However, in both cases recorded by Ernandez (1938) epistaxis, haematuria and melaena occurred in the early stages. Case 1 here reported had massive haematuria terminally, due to renal infarction, with severe colic. In the adult series purpura was only present in 37 per cent. of cases.

LYMPHADENOPATHY : This was present in 100 per cent. of the lymphatic and 76 per cent. of the monocytic series. In the former the process was generalized in 60 per cent. and in the latter in only 20 per cent. of cases. An attempt has been made by several writers, notably by Forkner (1934), to use the degree and quality of the glandular enlargement as a differentiating factor. He suggests that in the myeloid type the enlargement is slight or absent, in the lymphatic group generalized and of moderate or marked extent, and in the monocytic group moderate in the neck and slight elsewhere. We feel, however, that there is a much greater variation than this. There is no question that glandular enlargement is a more prominent feature of the lymphatic type. Nevertheless the most striking thing about the present first case was the wide distribution of the enlarged glands and the marked degree of their enlargement. Furthermore, in 26 per cent. of the lymphatic series the cervical glands were enlarged alone or were relatively greater in size. A rather higher proportion was found in the monocytic group. Mickulicz's syndrome was present in two cases, both of which were lymphatic in type. In both groups the glands were firm, discrete and painless. The extent of the enlargement would appear to vary directly with the duration of the disease.

ENLARGEMENT OF LIVER AND SPLEEN : A palpable spleen was present in 87 per cent. of the monocytic and 73 per cent. of the lymphatic series. This was rather an unexpected finding in view of the accepted idea that the spleen is always significantly enlarged in lymphatic leukaemia. Splenomegaly occurred alone in 26 per cent. of cases. Our first impression, that when enlargement of the liver occurred as well, it was the more obvious clinical feature, was not

borne out by statistics. Hepatomegaly occurred in 58 per cent. of the monocytic and 60 per cent. of the lymphatic series. In 20 per cent. of both groups enlargement of the liver was more evident than that affecting the spleen. In 13 per cent. of the monocytic and 17 per cent. of the lymphatic, neither were clinically enlarged. This clearly differs from the contention of Whitby and Britton (1937), for monocytic leukaemia as a whole, that the liver is invariably enlarged.

CUTANEOUS LESIONS : These are of some importance. They were present in 18 per cent. of the monocytic and in none of the lymphatic series. The lesions are of two types :

(a) Nodules in the skin, which are firm and painless and on histological examination show a preponderance of monocytic cells or their precursors.

(b) Widespread staphylococcal infection with boils or carbuncles. This seems to occur too frequently to be a coincidence. This feature was well illustrated by case 1.

GENERAL CONSTITUTIONAL FEATURES : These do not differ from those in other acute leukaemias. Pallor is well marked and associated with asthenia and weakness. Pyrexia is almost invariably present and may be of high degree. The presenting symptoms are many and varied ; the statement that they are usually associated with the mouth and fauces is not so true in childhood as in later life. The first thing noted is usually pallor and lack of energy. This may be accompanied by a sore throat or acute coryza. Purpura is often an early feature. Dyspnoea and abdominal pain have been noted in several cases ; the latter may be associated with melaena. Once established, the disease usually pursues a rapidly downhill course and the terminal stages are distressing. Two extremes, between which all gradations of severity exist, are represented by the two cases reported above. The first presents the subacute or remittent picture extending over a period of ten months. Glandular enlargement, splenomegaly, enlargement of the liver, purpura and, in fact, all the possible features were present to a marked degree. The child was relatively well during the earlier phases and rapid deterioration only occurred in the last three weeks. In the second case the child was apparently healthy until five weeks before death. Bleeding from the gums, enlargement of the lymph glands and purpura were never in evidence. The course was rapid and treatment failed to produce even temporary arrest of progress.

HAEMATOLOGY AND PATHOLOGY : Analysis of the clinical features suggests that there is no distinctive clinical picture in the monocytic leukaemia of childhood. This contrasts with Forkner's contention, after his study of the adult condition, that the clinical appearances are of sufficient value to allow a tentative diagnosis of acute monocytic leukaemia to be made independently of the blood picture. Similarly it fails to confirm the suggestion by Merklen and Wolff (1928) that clinically a strong presumption is possible. The striking difference between the present cases, together with a careful consideration of those reported in the literature, suggest that monocytic leukaemia shares its clinical features with other leukaemias of the acute or subacute types and cannot be diagnosed at the bedside without laboratory assistance.

During life it is possible to examine the blood and sternal marrow, and also, when an enlarged lymph node is available, this can be removed by biopsy. But leukaemia is a systematized disease of the reticulo-endothelial system, as has been stressed by one of us recently (Edward, 1938), and this can only be examined completely at autopsy. It is then possible to confirm the diagnosis of monocytic leukaemia by the distinctive histological appearances. We disagree with the statement of Beck (1938) that post-mortem findings do not materially help in the diagnosis of the type of leukaemia. Robb-Smith (1938) has pointed out that any confusion regarding the histology has arisen from the relative lack of attention paid to it, as compared with the detailed studies of the haematology. A full histological description has therefore been given of the present cases. The recognition of the histology is important because of the possibility of the hyperplasia of the reticular system occurring without escape of the newly-formed monocytes into the circulating blood (true aleukaemic monocytic reticulosis).

Special considerations

Interesting features about the two cases described in this paper are the relative scarcity of mature and immature granular leucocytes, both in the blood and in the tissues (although they were more numerous than in most cases of lymphatic leukaemia) and the stage of leucopenia in both. However, when the first case came under observation, the leucocyte count had risen and there were many typical immature monocytic cells. The blood and marrow films of these two cases have been carefully examined and compared with material derived from three other earlier cases at this hospital and from several adult cases. In both cases typical mature monocytes were scanty. The predominating cell was the promonocyte ; this had a mean diameter of $10\text{--}16\mu$, frequently contained one or two nucleoli, and conformed in every way to the published descriptions of this type of cell. There were also a few more primitive cells—monoblasts—measuring $13\text{--}16\mu$. In neither case could Auer's bars be found, despite a special search for them, and azurophil granules were scanty. In addition to the promonocytes and monoblasts there has been, in all the films examined, another type of abnormal cell classified as 'atypical.' These cells differ from the promonocyte in being smaller ($8\text{--}10\mu$) ; their nuclei are more darkly staining and contain no nucleoli. The shape of the nucleus is circular, polygonal or occasionally reniform ; the nuclear membrane is well marked and more regular than in the promonocyte. The cytoplasm is basophilic and scanty, the nucleus nearly filling the cell. In many ways these cells resemble lymphocytes, but their nuclei are larger and appear more immature. Between these cells and promonocytes and lymphocytes there are no hard-and-fast dividing lines and one group tends to merge into the other. These cells seem to have attracted little attention in the literature. Smith (1937) described abnormal cells of a third type in a case of monocytic leukaemia. These he called 'primitive cells,' as he believed them to be precursors of the monoblast. The cells studied by the present authors contain no nucleoli and do not appear highly

undifferentiated ; their appearance, in fact, differs markedly from the monoblast. On the other hand, all degrees of differentiation from the promonocyte can be made out, and it would seem likely that they are more closely related to the latter, perhaps resulting from abnormal activity of the leucopoietic system the function of which has been deranged by the leucotic process. The similarity of some of these 'atypical cells' to lymphocytes may indicate a close relationship between lymphocytes and monocytes. But a recent paper by Rhoads and Miller (1938) on the appearances of the bone-marrow in aplastic anaemia suggests that other small mononuclear cells exist, which have a superficial resemblance to lymphocytes, but differ in their origin and function. It is thus dangerous to identify a lymphocyte by a few of its striking morphological features.

The presence of these atypical cells is of importance in diagnosis. This is well exemplified in the second patient, in whom a large percentage of the abnormal cells were of this type. There were, however, enough typical promonocytes and monoblasts to indicate the true diagnosis. In this case supra-vital staining failed because of the paucity of leucocytes at the time of the examination and because many of them were 'atypical' cells. It would appear, from the findings in the first case, that the latter do not show the typical appearances of monocytes after supra-vital staining. It is of interest that in this patient half of the cells which flooded the circulation before death were 'atypical.' This markedly affected the histological appearances after death, because only a minority of the infiltrating cells and those in the blood-vessels were typical monocytic cells. Thus the occurrence of atypical cells confuses the diagnosis both haematologically and histologically. It is probable, therefore, that monocytic leukaemia is more common than is realized. The presence of a few typical promonocytes or monoblasts in a blood-film suggests the diagnosis, and post-mortem material must, as a routine, be carefully examined with an oil-immersion lens, especially after staining by Leishman's method, in order that this type of leukaemia is not missed.

Summary

1. Two new cases of monocytic leukaemia in childhood are described.
2. The clinical features of these and other recorded cases are analysed and compared with a similar series of the lymphatic type.
3. This analysis shows that there is no distinctive clinical picture. Certain minor differences exist, however, between the two types, notably the older age-incidence, longer duration, presence of cutaneous lesions, and, to a lesser degree, the distribution of the lymphadenopathy in the monocytic variety.
4. The diagnosis is established by haematological and histological investigation. During life examination of both blood and sternal marrow, together with a lymph gland where possible, should be carried out.
5. Attention is drawn to the presence of 'atypical' cells. Their occurrence in large numbers may confuse the diagnosis. It is suggested, in consequence,

that monocytic leukaemia is probably more common than is generally recognized at present.

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VITAMIN A REQUIREMENTS OF INFANTS: THE HEALTH OF INFANTS FED ON ROLLER-PROCESS DRIED MILK, WITH AND WITHOUT A SUPPLEMENT OF VITAMIN A

BY

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Some years ago the author (Mackay, 1934b) compared the progress made by two groups of infants fed on a roller-process dried milk, one group receiving extra vitamin A as an added supplement, the other wholly dependent for their vitamin A on that present in the dried milk, until such age as they received a mixed diet and derived part of their vitamin A from 'table food.' The comparison revealed no difference between the two groups except in one particular : the number of minor infective skin lesions in the control group was approximately double that in the group receiving extra vitamin A. The lesions classified as infective were for the most part due to some local irritation, where an infection (due to local organisms of low virulence) had presumably taken temporary root, e.g. sore buttocks, intertrigo.

A search of the literature on vitamin A deficiency in man revealed the fact that, although until recent years attention had usually been focussed on the lesions of the eyes, yet there was much to suggest that objective eye changes were often preceded by changes in epithelial cells in other parts of the body ; moreover, in clinical accounts of xerophthalmia and keratomalacia there was frequent mention of skin infections of various types (Mackay, 1934a). In recent years 'phrynoderm' or 'papular dry skin' has been recognized as part of the symptomatology of vitamin A deficiency in school-children and adults, and many of these cases have no clinical lesions of the conjunctiva or macroscopic epithelial changes in the eyes (Loewenthal, 1933 and 1935a ; Nicholls, 1934 ; Goodwin, 1934 ; Frazier and Hu, 1936 ; Reiss, 1936). In the light of these various observations the author (Mackay, 1934b) suggested that diminished resistance to skin infection was probably one of the earliest results of vitamin A deficiency in children. However, the number of infants with such infections in the two groups then studied was insufficient definitely to establish that the difference between the two groups could not have arisen by chance; although the uniformity of the differences obtained in each season and for the various types of skin lesion made this unlikely. The question is one of importance, both because it should be known whether in this country there is a risk of widespread, if slight, vitamin A deficiency in infants if they do not receive a supplementary ration of vitamin A, and also because it is highly

desirable that the earliest signs of this condition should be known. Potent vitamin D preparations nowadays often replace cod-liver oil as an antirachitic supplement, so that milk is often the only source of vitamin A in the diet of infants.

As against the author's findings, Hess, Lewis and Barenberg published in 1933 an account of an investigation, similar to the author's, but carried out on in-patients in the Home for Hebrew Babies, New York. They concluded that the babies who received the usual diet of this institution, without a supplement of cod-liver oil or any vitamin A concentrate, did not show any evidence of vitamin A deficiency or of increased susceptibility to skin infections. In 1938 Lewis and Barenberg published another paper from this home. Two groups of babies were given a diet consisting of a partly skimmed dried milk (which when reconstituted contained 1·5 per cent. fat) up to the age of four months, after which semi-solids and solids gradually replaced part of the milk. Certain rich sources of vitamin A, such as spinach, butter and egg, were excluded. One group received in addition to this basic diet a supplement of halibut oil, which greatly increased their vitamin A intake. No difference was found in the nutritional status or in the incidence of infections between the two groups—and no excess of skin infections in the group getting partially skimmed milk. The authors give no indication of how they assessed the skin infections. They conclude that the ordinary diet of the home, which provided each child daily with one to two ounces of full milk per pound of body weight, with the addition of vegetables, butter, and eggs, as the child grew older, allowed an ample margin of safety as regards vitamin A without the administration of cod-liver oil. However, it should be stated that the average time a baby was on the partly skimmed milk without other sources of vitamin A was under four weeks, since the average age of babies at the beginning of their observation was a little over five months, and by six months old they were having vegetables. The result, too, may have been influenced by whether or not the babies had built up vitamin A reserves before five months old (e.g. by cod-liver oil medication before they came under observation).

In recent years the author has tried to ascertain whether, in older children of the hospital class in London, an extra ration of vitamin A will diminish infective skin lesions or bring about their more rapid cure. Unfortunately this work has not produced positive results :

(1) Vitamin A was given to children attending hospital with skin infections (unpublished work), but so many factors entered into the results that no clear conclusion could be reached.

(2) Children admitted to hospital with measles were treated with vitamin A. They showed no superiority over the control group in resistance to skin infections or in any other respect, but their average stay in hospital, and consequently the average period of treatment, was too short for any final conclusions to be drawn as to the possible effect of extra vitamin A on their skins (Mackay, Linford, Mitman and Wild, 1936).

Workers studying clinical cases of overt vitamin A deficiency in East Africa (Loewenthal, 1935b) and in China (Sweet and K'Ang, 1935; Frazier and Hu, 1936 ; Reiss, 1936) did not find evidence of the existence of increased susceptibility to skin infections in their cases. The author decided, therefore, to repeat the investigation with babies given roller-process dried milk with and

without a supplement of vitamin A, and particulars of this work are given in the present paper.

Nature of present investigation

This investigation lasted nearly three years, and as before was concerned with artificially-fed babies and young children up to two years of age living in their own homes. A few babies received some breast milk. The babies were divided into two groups, the conditions for each group being kept as similar as possible except for the factor under investigation. The control group received only the vitamin A present in their dried milk or mixed food, and were given an emulsion of vitamin D ; the group with which they were compared received extra vitamin A as well as D in the form of an emulsion of cod-liver oil.

Clinical material.—The children were out-patients at the Queen's Hospital for Children, which is in a poor district in London, and as before children of the poorest social classes were included.

NUMBER OF BABIES.—The number of babies originally started in the investigation was 145, but only 102 were eligible for the final comparison : i.e. 49 infants given extra vitamin A, and called for brevity the 'A group,' and 53 controls.

No child was included who did not attend and receive the vitamin emulsion for at least four weeks. The majority of the 43 children excluded either did not attend long enough or did not receive sufficiently regular treatment. Some are omitted for other reasons, such as the giving of cod-liver oil to a control by a mother, or evidence of a condition which would influence normal development irrespective of the diet, e.g. one child proved to be a midget and another had tuberose sclerosis.

AGE OF INFANTS.—All infants were under five months old when first included in the series ; and over three-quarters of them were under three months old. The age distribution of the 102 cases was as follows : under one month old, 8 cases (7.8 per cent.) ; one to two months old, 34 cases (33.3 per cent.) ; two to three months old, 36 cases (35.3 per cent.) ; three to four months old, 21 cases (20.6 per cent.) ; four to five months old, 3 cases (2.9 per cent.). The oldest child at the end of the observation was twenty-seven months old.

PERIOD OF ATTENDANCE.—The period of attendance varied from thirty-five days to nearly twenty-six months, and averaged 8 months 23.7 days.

CLINICAL CONDITION OF THE INFANTS.—Nearly all the children were under normal weight when first included, and many were in poor condition. The commonest reason for attendance at hospital was underfeeding or feeding difficulties (with complaints of vomiting, fretfulness), but 20 of the total 102 suffered from some infection, such as bronchitis, otitis media or whooping cough when first seen. Very few had had any cod-liver oil or other vitamin A supplement. The average birth weight was 7 pounds 0.7 ounces.

The great majority made good general progress while under observation.

ECONOMIC STATUS OF THE FAMILIES.—The majority of the fathers, as in the previous investigation, were manual workers, a number were casual labourers or unemployed, whilst others were small shop-keepers and skilled workers in better circumstances. Many parents received public or charitable assistance in the form of milk grants or monetary help.

ATTENDANCE OF INFANTS.—The babies were usually examined naked at fortnightly intervals, and many attended very regularly. A child who did not attend for six weeks was considered to have ceased to attend.

The diet given.—The diet was similar to that given in the previous investigation, but mixed feeding was started rather earlier. Up to six months old, the infants received dried milk, with added sugar, iron and orange-juice. The babies in the control group were given an emulsion of vitamin D, those in the A group an emulsion of cod-liver oil to provide vitamin D and vitamin A. Mixed feeding was started between six and seven months old, and in the course of about four to five weeks the child's milk ration was reduced to about one to one and a quarter pounds in the week (say about one pint or half a litre daily) and the baby was given fish on two or more days weekly, three or more eggs in the week, and fruit daily, besides cereal foods, vegetables, and gravy. Between eight and ten months old most children were started on meat. In the previous investigation mixed feeding was started between seven and eight months old, so that in the present work babies received food containing vitamin A, other than milk, about one month earlier.

DRIED MILK AND SUGAR.—The same brand of dried milk* was used as in the previous work—i.e. a full-cream roller-process dried milk incorporating iron and ammonium citrate. This time no vitamin D or vitamin A was added to the milk before drying, as was done in the previous investigation. The dried milk was sold to the mothers at hospital at cost price, or, if the mother, on account of poverty, was eligible to a milk grant from the borough, she was asked to exchange the dried milk she received from the borough for the special dried milk at hospital. Many mothers, however, obtained their dried milk at welfare centres, in which case it was not possible to keep a check on the quantity consumed. Up to six months old, each baby received daily 60 to 90 calories in added sugar and the rest of its calorie needs in dried milk ; by six months old he was usually having one and three quarters to two pounds of dried milk in the week, say nearly one and three quarter pints or about one litre of milk daily. After seven months old the milk allowance was decreased to about one pound of milk powder or a little more weekly.

IRON.—Each pound of dried milk contained $3\frac{1}{2}$ grains of iron and ammonium citrate, a quantity found sufficient to prevent nutritional anaemia (Mackay and Goodfellow, 1931). The haemoglobin levels of the babies in the A group were estimated monthly (as this group served also as controls in another investigation), and in a few cases where the mother was not buying iron-containing dried milk * at the hospital a slight grade of anaemia developed.

* Hemolac, Messrs. Cow and Gate, Ltd.

It is probable that in these cases the mothers did not give their infants the milk prescribed. Nevertheless the haemoglobin level from five to eighteen months old averaged 82 per cent. in the A group, and it can be concluded that the great majority of both groups received sufficient iron.

VITAMIN C.—One teaspoonful and upwards of orange juice daily was advised for each baby. After six months old, various fruits and vegetables were given.

VITAMIN D.—Every baby was ordered an extra supplement of vitamin D. The controls were ordered 1575 international units daily in the form of an emulsion containing irradiated ergosterol (obtained from the British Drug Houses), 60 minims being given three times daily. The A group were ordered 60 minims three times daily of a 50 per cent. emulsion of cod-liver oil, supplying a minimum of 580 units daily. No definite evidence of rickets, clinically or radiologically, was found in any child in the series. Forty skiagrams of thirty children of susceptible ages made in the late winter and spring months showed one child in each group with some cupping or irregular calcification at the distal end of the ulna, which was probably evidence of mild rickets already healed ; but the change was extremely slight.

Vitamin A in the diet.

VITAMIN A IN THE DIET OF CONTROLS.—The quantity of vitamin A in the dried milk was not estimated during the present investigation. In the earlier investigations the vitamin A value was estimated several times in terms of cod-liver-oil-equivalent by the biological and antimony-trichloride methods. There were obvious discrepancies in the results. Two examples are given : (a) One pound of dried summer milk was estimated by the biological method to contain the equivalent of 13 grammes of cod-liver oil of 12·0 blue value, and by the colorimetric test the equivalent of 2·1 c.c. of cod-liver oil of 7·5 blue value, both estimations being made on samples from one batch of milk. (b) When comparing the A value of two samples of milk, to one of which vitamin A had been added, there was approximately a tenfold discrepancy between the biological and colorimetric tests, and the differences were not consistent (Mackay, 1934b). A sub-committee of the British Pharmacopoeia Commission (1936) has published data demonstrating the wide limits of error of the biological test. From this it was obvious that no conclusion could be drawn from a comparatively small number of tests as to the relative vitamin A values of dried milk supplies over different years, and therefore such tests were not repeated during the present investigation.

However, as the source and method of preparation of the dried milk was the same, and individual variation in cows supplying the milk would probably be smoothed out by the pooling of milk from different herds, there was no reason to anticipate a difference in A value over the two periods.

VITAMIN A CONTENT OF DIET OF A CASES.—The earlier investigations showed that those babies whose supply of vitamin A was solely derived from their dried milk, though they were thought to have a slight deficiency of vitamin A,

certainly suffered from no gross deficiency. Hence even a small addition of vitamin A to the diet should have ensured a sufficiency of this vitamin. All the vitamin A group were ordered 90 minims daily of cod-liver oil obtained from Messrs. Allen and Hanbury. This was given as a 50 per cent. emulsion, 60 minims three times daily. One pound of the dried milk used in the previous investigation was estimated (average of six tests) to contain as much vitamin A as about 10 grammes of one of the standard cod-liver oils used. The dosage of cod-liver oil ordered in the present investigation was approximately 40 grammes weekly, supplying a minimum of 32,000 units weekly—say 4600 international units daily. Hence it was presumably ample to ensure a sufficiency of vitamin A. After six months old, when babies were given mixed feeding, their sources of vitamin A were multiple.

Results

The children in the control group and in the A group were fairly evenly matched at the outset of the investigation (see table 1). In round figures the average weight at first attendance differed by only $\frac{1}{4}$ ounce and was just over 9 pounds; the average age differed by five days and was about $2\frac{1}{4}$ months; and the balance of sexes was not dissimilar: in the control group 64 per cent., and in the A group 59 per cent. were males. The average duration of attendance was, however, longer in the A group. These infants attended for an average period of 9 months 14·2 days, against 8 months 4·7 days in the control group, a difference of about $1\frac{1}{3}$ months; so that the A cases at the end of the observation period averaged nearly $1\frac{1}{2}$ months older than the controls. In the matter of infections the scales were weighted slightly against the controls, for 26 per cent. of them had at the outset some infection, e.g. bronchitis (7 cases), whooping cough (1 case), enteritis (3 cases); whereas in the A group only 12 per cent. had infections. The birth weight, as stated by the mothers, averaged 7 pounds 1·5 ounces for the controls and 6 pounds 15·7 ounces for the A cases.

Weight.—Judged by weight (see table 1) the great majority of babies in both groups made good progress. Taking both groups together, babies attending at five months old averaged 14 pounds 2 ounces in weight and at twelve months they averaged 21 pounds 7 ounces. They started well under Holt's standard weight curve, but from eight months old and onwards were above it. Taking the two groups separately the average weekly gain of each over the whole period was similar, vitamin A cases 4·35 ounces weekly, controls 4·24 ounces weekly, a difference of only about 0·1 ounce weekly, or under $\frac{1}{2}$ ounce monthly. Since the A cases averaged about $1\frac{1}{2}$ months older at the end of the observation period, and the normal rate of gain diminishes at about the sixth month, age should have given the controls a slight advantage. This was probably set off by the fact that a larger proportion of the controls had an infection when first seen. If the groups are subdivided by season, the vitamin A cases show slightly superior growth in one season, the controls in the other, in each case (as would be expected if other factors were equal) the younger age group show the larger

TABLE I
THE AGES AND WEIGHTS OF THE VITAMIN A CASES AND CONTROLS COMPARED

WHOLE PERIOD	NO. OF CASES	SEX		AVERAGE AGE		AVERAGE ATTENDANCE		AVERAGE WEIGHT		AVERAGE TOTAL GAIN	AVERAGE WEEKLY GAIN										
		M.	F.	FIRST ATTENDANCE	LAST ATTENDANCE	FIRST ATTENDANCE	LAST ATTENDANCE	FIRST ATTENDANCE	LAST ATTENDANCE												
A Cases	49	29	20	mth. 10·6	days 2	mth. 11	days 10·4	lb. 9	oz. 1·2	lb. 11·20	oz. 0·6										
Controls	53	34	19	5·7	2	10	10·4	9	1·9	18	6·1										
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SUB-DIVIDED BY SEASONS		NO. OF PERIODS *																			
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SUMMER (3 SEASONS)																					
A Cases	49	5	12·5	8	27·4	3	14·9	13	6·3	17	12·3										
Controls	43	6	15·5	10	8·3	3	22·8	14	13·6	18	14·1										
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WINTER (3 SEASONS)																					
A Cases	71	6	19·7	10	26·2	4	6·5	14	9·2	19	4·4										
Controls	72	5	18·1	9	9·4	3	21·3	13	4·6	17	10·6										
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* In the seasonal subdivisions, children attending during more than one summer or winter period cause the number of 'periods' of attendance to be in excess of the number of children attending.

weekly gain. Hence it may be said that added vitamin A did not increase the rate of growth.

Morbidity rates.—(a) **GENERAL.**—The general morbidity rate was assessed in the same way as described in other papers (Mackay and Goodfellow, 1931; Mackay, 1934b). There is undoubtedly a subjective element in such counts, but carefully carried out, with the case sheets of the two groups intermingled to prevent risk of a change in standard between the assessment of one group and the other, there is no doubt that they give a fair comparison. Table 2 shows that the morbidity rates were closely similar for all illnesses ; and this holds good for illnesses of the respiratory tract, diseases of the intestinal tract and specific fevers when estimated separately.

TABLE 2
GENERAL MORBIDITY RATES—VITAMIN A CASES AND CONTROLS
COMPARED

	VITAMIN A CASES		CONTROLS	
	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS
No. of infants	49		53	
Average attendance	9 months 14·2 days		8 months 4·7 days	
No. of child-months	464 ¹ ₀		432 ³ ₁ ⁰	
DISEASE	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS
Respiratory tract— Cold in head or sore throat	57	12·3	53	12·3
Bronchitis	30	6·5	33	7·6
Pneumonia	1	0·2	0	—
Otorrhoea	5	1·1	6	1·4
Gastro-intestinal— Diarrhoea and vomiting, or either	19	4·1	24	5·6
Other diseases— Specific fever	8	1·7	5	1·2
Not otherwise classified	2	0·4	2	0·5
Totals	122	26·3	123	28·4

Hence added vitamin A did not reduce the general morbidity rate.

(b) **LESIONS AFFECTING SKIN, MOUTH AND EYES.**—In the course of the author's previous investigations, attention was not concentrated on lesions of the skin, but analysis of the figures after the completion of the clinical observations showed that whereas non-infective skin lesions were approximately equally common in the two groups, the infective skin lesions were about twice as common in the control group as in the A group. Consequently when the investigation was repeated, careful notes were made of all skin lesions, and many minutiae

were counted. Moreover, if a skin lesion, e.g. chapping of the buttocks, lasted for over one month after it was first observed, it was reckoned twice and counted as two lesions, if it persisted into the third month as three lesions, and so forth. Hence the totals for skin lesions in this investigation are much larger than in the earlier one.

Under infective skin lesions are included pustules, boils, infected scratches, and all excoriations of the skin whether resulting from discharges (e.g. nasal discharge or ear discharge) or from dribbling or from irritation of the napkin area. Such excoriations are reckoned as infective on the assumption that they are due to local irritation together with infection by local organisms of low virulence.

TABLE 3
LESIONS OF SKIN, MOUTH AND EYES—VITAMIN A CASES AND CONTROLS COMPARED

	VITAMIN A CASES		CONTROLS	
LESION	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS	NO. OF ATTACKS	NO. PER 100 CHILD-MONTHS
SKIN				
Infective—				
Excoriation, pustules, boils, intertrigo, external otitis, etc.	79	17·0	70	16·2
Non-infective—				
Erythema, peeling, chapping, papules, sudaminal rashes, urticaria	191	41·0	189	43·7
MOUTH				
Thrush or other stomatitis, ulcer or cracked lip	7	1·5	8	1·9
Geographical tongue	3	0·6	0	0
EYES				
Conjunctivitis, blepharitis, styes	9	1·9	6	1·4
Totals	286	62·2	273	63·1

Table 3 sets forth the comparison. In each sub-division of the skin lesions the figures are similar for the two groups of children. The addition of vitamin A to the diet did not diminish the incidence of either infective or non-infective

skin lesions. As before, no difference was found in the texture of the skin in the two groups.

The incidence of infections of the mouth and of the eyes is small, and of a similar order in both groups—so that the addition of vitamin A did not diminish these lesions. Geographical tongue has been included under mouth infections, although admittedly its etiology is uncertain. Its omission, however, would make no difference to the conclusions, since the number of cases is small.

Discussion

The results of this investigation have been wholly negative—the controls and the group given extra vitamin A were similar in rate of growth and general progress, in general morbidity rates, and in the incidence of infections of the mouth and eyes, as well as in the incidence of skin lesions, whether infective or non-infective, and also in skin texture. It must be concluded, therefore, that in 1935–38 the roller process full-cream dried milk used supplied sufficient vitamin A for the child's needs up to six months old, and that thereafter the smaller ration of milk together with the addition of other food was still sufficient for all the child's needs of vitamin A. The milk used in this work was from the same source and put through the same processes as that used in the earlier investigation, and so, *a priori*, would be likely to contain a similar amount of vitamin A.

However, the vitamin A value of fluid cow's milk apparently shows wide variation—Willstaedt and With (1935), summarizing the findings of different authors, say that these vary between 15 and 700 international units per 100 c.c. On the other hand, Sherman (1937), who gives an average value of 292 ± 12 international units per 100 grammes (or 1708 units per pint), considers that as the probable error of this figure is only 4 per cent. of its value, the figures in the literature give 'a very exaggerated impression of the extent to which the vitamin A values of milk' varies. For the ordinary reader, however, the variations in the estimates of vitamin A value seem chaotic and one concludes that many estimates must be erroneous.

The estimates of vitamin A requirements will now be considered. Booker (1938) from an examination of the available data suggests that for an adult the minimum requirement of vitamin A to preserve normal vision (*i.e.* normal dark adaptation) is 20–30 international units per kilogramme of body weight. Guillet, Miller and Hughes (1937) have reached the conclusion that this 'minimum requirement' per unit of body weight is probably the same for different species of animals, for young animals and old, and for the gestating female. They find, however, that the minimum necessary to produce normal vision and normal growth will not ensure normal reproduction or allow of storage of the vitamin. They suggest that five to ten times the so-called 'minimum requirement' as judged by the preservation of normal dark adaptation is actually 'a desirable minimum to set for practical purposes,' and even this will result in the lactating female producing a milk low in vitamin A values. On the basis that 10×25 international units is required per kilogramme of body weight, a baby of 9 pounds or 2 kilogrammes body weight would require 1000 international units daily.

Can it be stated if the control cases in the author's investigation are likely to have received less than this amount? Averaging six estimates (three biological and three by the antimony-trichloride method) of the vitamin A value of the dried milk used in the previous investigation, the result is obtained that one pound of this dried milk was equivalent in vitamin A value to 10·4 grammes of one of the standard cod-liver oils used. If it can be assumed from these data that one pound of the dried milk had a vitamin A value of at least 6000 international units, then the A value of one pint of reconstituted milk would be approximately 1000 units. A baby weighing 9 pounds and consuming about one pound weekly of dried milk would get about 1000 international units of vitamin A, i.e. its theoretical requirement on the basis taken in the calculation above. But as there was a six-fold difference between the lowest and the highest estimation of vitamin A value made by one method (the antimony-trichloride test) there still appears to be uncertainty in this estimation.

Meulemans and de Haas (de Haas and Meulemans, 1936; Meulemans and de Haas, 1938) approach the question of vitamin requirement from a different standpoint. They find that the vitamin A value of the milk of women of good income-level is considerably over double the vitamin A value of the milk of cows fed on pasture, and is, say, six times the value of that of stall-fed cows. They argue from this that dairy milk is unlikely to contain sufficient vitamin A to meet the infants' needs, and that all artificially-fed babies should be given a vitamin A supplement.

Thus it still remains unproven whether or not increased susceptibility to skin infections is an early symptom of vitamin A deficiency, and in the author's opinion it seems probable that the milk used in the earlier work did in fact contain less vitamin A, and that this quantity was insufficient for the babies' needs. In favour of this, to quote from the previous paper, is the fact that the difference in incidence of skin infections : '(a) is statistically significant between the total groups ; (b) shows itself both in the total number of 'attacks' and in the number of children affected, so that it is not only a question of some few children having repeated attacks ; (c) is apparent in each seasonal sub-division of the total groups ; and (d) is apparent in each sub-division for the different types of lesions, though figures are admittedly small in these sub-divisions.'

The work of Lewis and Barenberg (1938), already described, does not support this view. They estimate that the half-cream dried milk they used had a vitamin A value of 325 international units per pint of reconstituted milk. The fact that they found no evidence of vitamin A deficiency when using this partly skimmed dried milk will certainly suggest to many that a full-cream dried milk, such as used in the present work, must provide a sufficiency of vitamin A. But the half-cream milk was not tested out as the sole source of vitamin A. Their babies averaged over five months old at the beginning of the observation. Semi-solids were started at four months old and by six months all were getting vegetables providing extra vitamin A. Hence the average time during which their babies depended solely on their milk as a source of vitamin A was under one month. Xerosis of the conjunctiva takes three to four months to develop

in very young babies fed on a grossly deficient diet, i.e. machine-skimmed dried milk (Forest and Wolff, 1932), though it is not suggested that xerosis is the earliest symptom of vitamin A deficiency. There is no information as to whether or not many of their babies might have built up their reserves of vitamin A by getting cod-liver oil or other vitamin supplements before starting the observation.

On the other hand, the babies in the present author's earlier London observations averaged less than three months old at the start; extremely few had any vitamin A supplement when first taken on, and they had an average period of four to four and a half months to run on bottle feeds, during which time they were entirely dependent on the dried milk for vitamin A. Hence if the milk were deficient in vitamin A, then the London babies had a very much better chance of showing it than the New York babies.

The criticism will probably be made that the vitamin A content of the milk used in the present investigation should have been determined. In answer to that it may be said that, in view of the discrepancies in the laboratory tests carried out in the earlier work, it is improbable that more tests would have established a small difference between the milks used in the two periods, if such did exist.

The practical conclusion to the author's two investigations would seem to be that, pending other evidence on the subject, it is advisable to supply infants with a daily supplement of cod-liver oil or other potent source of vitamin A, in spite of the fact that the roller process dried milk used in the second observation has been proved to supply all the vitamin A required by the infant.

Summary

The results of an investigation carried out some years ago on a series of London babies seemed to indicate that they suffered from a slight grade of vitamin A deficiency, manifested by an increased susceptibility to minor skin infections (Mackay, 1934b). These babies were given roller-process dried milk, which was their sole source of vitamin A up to seven or seven and a half months old. According to the (tentative) estimate put forward the vitamin A value of this milk when reconstituted was not less than 1000 international units per pint, so that a baby of about 9 pounds body weight would have received, say, 1000 international units daily, and a baby of 17 pounds nearly 2000 international units daily. This work has now been repeated.

Between August, 1935, and March, 1938, two groups of babies were kept under observation in the out-patient department of the Queen's Hospital for Children. The average age at first attendance was a little over two months, and the average duration of attendance 9 months 14 days and 8 months 5 days respectively. All babies were fed on full-cream dried milk prepared by the roller process and obtained from the same sources as in the previous investigation. A few babies received some breast milk. All were ordered supplements of iron and ammonium citrate, vitamin C in orange juice, and vitamin D.

Approximately half (49 babies) received cod-liver oil supplying vitamin A as well as vitamin D, the rest (53 babies) received vitamin D as an emulsion prepared from irradiated ergosterol and no extra source of vitamin A. After six months old the babies were started on solid food.

Results.—The progress of the two groups of babies was closely similar in all the points examined : i.e. in rate of gain in weight ; in general resistance to infection, and in resistance to infections of the mouth, eyes and skin ; in incidence of non-infective skin lesions, and in texture of the skin. The roller process dried milk used, therefore, supplied a sufficient amount of vitamin A to meet the infants' needs.

This work does not negative the author's previous findings, which suggested that roller-process dried milk did not fully meet the infants' requirements of vitamin A, as, for reasons stated in the paper, it cannot be affirmed that the vitamin A content of the milk was the same over the two different periods. It is suggested that, pending other investigations on the subject, it is desirable to give artificially-fed babies a supplement providing extra vitamin A.

As yet little evidence exists concerning the quantitative needs of the infant in vitamin A (Booker, 1938), and estimates of the vitamin A value of milk show excessively wide variations (Meulemans and de Haas, 1938).

The author's sincere thanks are due to all those who helped with the clinics at the Queen's Hospital for Children, particularly to Sister F. M. Westbrook for her constant help and co-operation throughout the work, to Miss M. Wright, who undertook all arrangements for necessitous cases, and to Miss L. E. Jacob, M.P.S., and the dispensary staff.

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A REVIEW OF TWENTY YEARS OF BREAST FEEDING IN LIVERPOOL

BY

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Spence (1938) in a recent address made the following statement :

' Accurate information about the incidence of breast-feeding is difficult to find, and is still more difficult to compare on account of the difference in the methods of enumeration used. We desire to know what proportion of babies in various countries or in different social groups are breast- or artificially-fed from birth. We desire to know also at what age weaning takes place. It is this precise information which is lacking.'

As medical officer in charge of an infant welfare centre I have endeavoured in this paper to provide some of the information asked for. During the past year I had been impressed by the apparently large proportion of bottle-fed babies seen at the clinic. I thought this might be associated with the fact that breast-fed babies rarely require medical attention. In order to determine whether or not this impression was correct, I noted the feeding in a hundred consecutive cases seeking advice during two weeks in last October, and found that 41 per cent. were breast-fed and 59 per cent. bottle-fed.

While working under several other public health authorities, I had noticed that the incidence of breast-feeding seemed to vary from place to place. It appeared to be lowest in the depressed industrial areas and highest in the rural districts where cows' milk is difficult to obtain owing to the Milk Marketing Schemes, and dried milk can only be procured at the welfare centres, which are necessarily rather scattered. The time of weaning also varied considerably, ranging from nine to eighteen months according to the custom prevailing in the locality.

In an attempt to ascertain if there is any real decline in breast-feeding as has been suggested, the case sheets in the clinic were collected and examined for definite information. The clinic at which I am now working was opened in 1930, and it was decided to begin the investigation on the figures of that year, but later it was found that records for as far back as 1917 could be obtained. A total of 735 cases attended during 1930. Out of these, in 499 the case records were sufficiently complete for working out statistics ; 191 cases ceased attendance during the progress of breast-feeding, and the remaining 45 were also rejected in view of the fact that the babies were either only partly breast-fed

or the notes were incomplete. Then the records for 1934 were similarly dealt with, the intention being to compare the figures for four-yearly intervals. As the figures for 1938 could not be accurately assessed until all the babies born in that year were nine months old, the year 1937 was taken instead. To complete the four-yearly sequences the figures for 1918, 1922 and 1926 were similarly examined. A certain number of incomplete notes had to be discarded. Owing to the different methods of enumeration used by other workers, it was decided to give two comparative tables for the six years under consideration showing :

(a) The percentage of the babies born each year who were breast-fed during each month of the period of lactation (table 1).

TABLE I
PERCENTAGE OF BABIES ON THE BREAST DURING THE FIRST EIGHT WEEKS AND SUBSEQUENTLY UP TO THE NINTH MONTH

DURATION	1918	1922	1926	1930	1934	1937
At birth	100	100	100	100	100	100
1 week	82	86	87	92	96	93
2 weeks	79	83	84	90	93	86
3 "	76	75	77	81	85	78
4 "	74	69	71	76	80	71
5 "	70	66	65	70	71	64
6 "	67	63	61	68	68	61
7 "	61	58	56	63	65	57
8 "	58	55	52	62	64	54
3 months	52	51	46	56	52	48
4 "	42	41	31	46	43	37
5 "	36	36	26	42	37	33
6 "	33	32	23	37	35	29
7 "	29	29	21	33	29	25
8 "	27	26	19	31	26	23
9 "	22	22	15	27	18	15
Over 9 months	11	11	9	14	5	4

(b) The percentage weaned during each month (table 2). The figures will be slightly lower than those of other investigators because the defaulting and doubtful cases are not included. In addition, the statistics for each year indicate only those babies born in it, and not merely those attending in it. If the latter method had been used, it would have been difficult to assess the results accurately.

The only other investigation of this nature which I could find had been carried out by Garland and Rich (1930) in America. Table 3 shows their results compared with those of Liverpool in 1930.

Fig. 1 shows how the six years coincide, and that the incidence in 1926 is lowest, while that in 1930 is highest. Fig. 2 indicates that there is a tendency in recent years to an increase in breast-feeding during the first, second, fourth and fifth months ; it remains stationary during the third, seventh and eighth months ; while from nine months onwards there is a decline. Only three graphs are given, as the others for the same period are similar. I am unable to suggest any reason why in 1930 the incidence should be high and in 1926

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it should be low. Several different medical officers have been in charge of the clinics. The cases up to 1926 were taken from all the welfare centres in Liverpool, and from 1930 onwards from one centre only. These latter patients are those who were moved out from the old clinic areas to a new housing estate, and are essentially the same social class, but in a new environment.

TABLE 2

THE PERCENTAGE OF BABIES WEANED IN EACH OF THE SIX YEARS UNDER CONSIDERATION IS GIVEN FOR EACH WEEK FOR THE FIRST EIGHT WEEKS, AND FOR EVERY MONTH THEREAFTER UP TO NINE MONTHS. THE NUMBERS UTILIZED AND DISCARDED, AND THE TOTAL NUMBER OF CASE SHEETS OBTAINED FOR EACH YEAR ARE GIVEN BELOW

DURATION	1918	1922	1926	1930	1934	1937
At birth	17.6	14.2	13.7	7.6	4.2	6.6
1 week	2.7	3.0	2.5	2.0	3.2	7.0
2 weeks	3.4	7.9	6.9	8.9	8.3	8.4
3 "	2.0	6.0	5.5	4.9	4.8	6.8
4 "	4.4	3.4	6.1	6.4	9.4	7.2
5 "	2.7	3.07	3.3	2.4	2.7	2.5
6 "	5.8	4.6	4.8	4.7	2.5	3.8
7 "	2.7	3.3	3.5	1.2	0.38	2.9
8 "	6.2	4.1	6.1	5.6	12.3	6.3
3 months	10.3	10.3	15.0	10.1	9.4	10.7
4 "	5.5	4.8	4.5	3.7	5.7	4.3
5 "	3.4	3.5	3.2	4.7	3.2	3.6
6 "	3.7	3.0	2.1	4.1	5.5	4.3
7 "	2.4	2.9	2.0	1.6	3.0	2.0
8 "	5.1	3.4	3.7	3.9	7.7	7.7
9 "	10.6	10.8	6.4	12.8	13.1	10.7
Over 9 months	11.2	11.8	10.7	15.4	5.5	5.2
Number utilized	294	784	977	499	518	439
Number discarded	164	370	592	236	159	97
Total for year	458	1154	1569	735	677	536

TABLE 3

COMPARISON OF PERCENTAGE OF BABIES WEANED AT VARIOUS AGES

	LIVERPOOL, 1930 (CLINIC)	GARLAND AND RICH, 1930 (PRIVATE)
At birth	0.0	0.0
1 week	9.6	9.0
4 weeks	20.3	16.0
2 months	15.0	9.0
3 "	10.1	7.5
4 "	3.7	6.0
5 "	4.7	1.0
6 "	4.1	4.5
8 "	5.5	14.5
1 year	25.7	18.0
Over 1 year	1.3	14.5

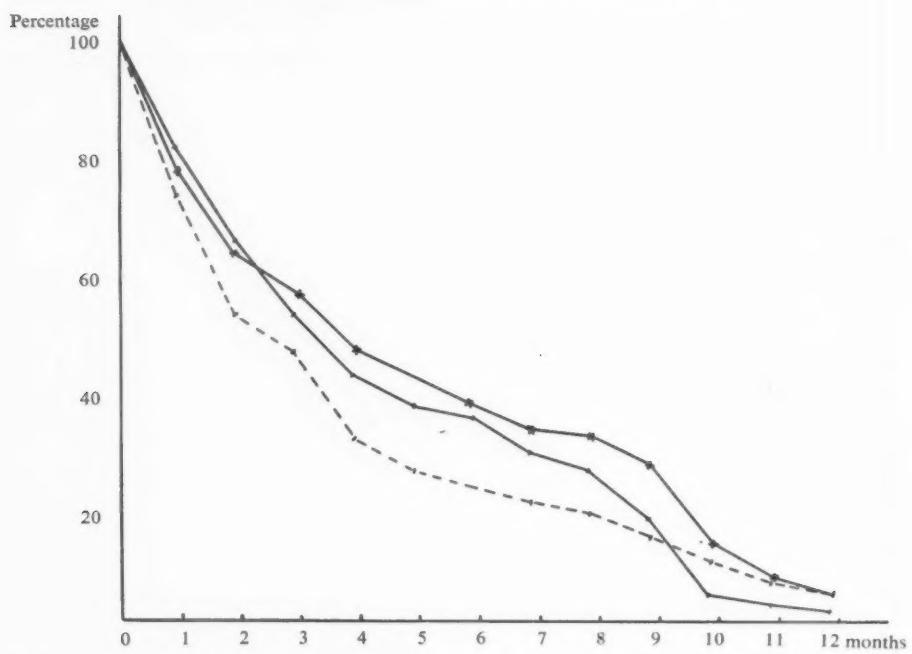


FIG. 1.—1926 —— 1930 ······ 1934 ×—× 1937 ······. For the sake of clearness 1918, 1922, and 1937 are not given, as they are in many points similar to 1934.

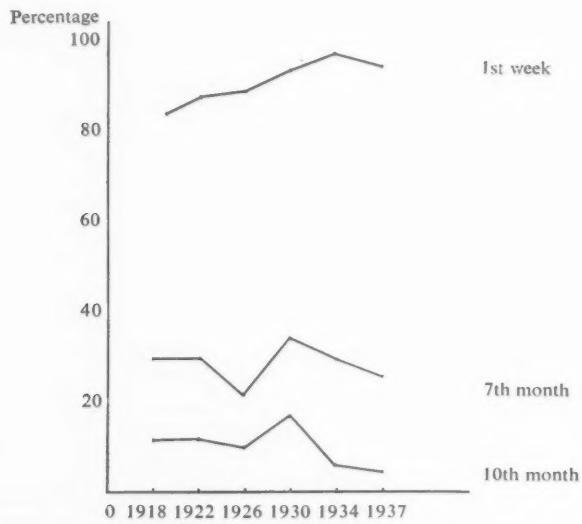


FIG. 2.—Comparing breast-feeding during 1st week, 7th and 10th months of each year investigated.

There are certain mothers in the district who never attend the clinic, but who are visited in their homes by the health visitors. I thought that there might be a higher rate of breast-feeding among these women and asked one of the health visitors for her records for 1937, which concerned 229 babies. From these the following figures were obtained.

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During the first week 91·3 per cent. were breast-fed ; at the beginning of the second month 62·7 per cent. ; at four months 25·5 per cent. ; at the end of nine months 3·4 per cent. Comparison of these figures with those for the clinic in the same year (1937) shows that they are almost identical.

Therefore it is inaccurate to say that welfare clinics encourage an increase in bottle-feeding.

In 1922 Ida Winternitz came to the conclusion that the capacity for breast-feeding is not hereditary. Table 4 shows her percentages as compared with

TABLE 4
COMPARISON OF THE RESULTS OF AN INVESTIGATION INTO FAMILY HISTORIES : PERCENTAGE OF BREAST-FED BABIES IN VARIOUS GROUPS

AUTHOR	AMONG MOTHERS WHOSE DAUGHTERS WERE GOOD NURSES	AMONG MOTHERS WHOSE DAUGHTERS WERE POOR NURSES	AMONG DAUGHTERS WHOSE MOTHERS HAD BREAST FED	AMONG DAUGHTERS WHOSE MOTHERS HAD NOT BREAST FED
Bunge ..	99·2	43·2	53·2	0·7
Winternitz ..	86·7	91·8	60·8	73·3
Robinson ..	86·6	65·0	76·4	52·6

Bunge's and the present series. Mothers are divided by her into two classes. Those who nurse for less than three months are called poor nurses and those who feed for over three months good nurses. The present series was divided in the same manner and consisted of a hundred consecutive new cases (excluding primiparae) who have started attending the clinic since last October. It will be seen that when the mother has breast-fed, three-quarters of the daughters have done likewise ; and when the mother bottle-feeds, about half the daughters do the same. This suggests that parental opinion rather than heredity may play a part in influencing the mother in the method of feeding her child. This surmise is further substantiated by the following data from the 1934 records. It was found in that year that of a hundred mothers living in apartments, 65 per cent. had weaned their babies before the end of two months, compared with a hundred consecutive cases living in houses of whom only 43 per cent. had ceased breast-feeding within the first two months. These cases were further analysed.

100 cases in rooms	{ 67 primiparae { 20 breast-fed. 47 weaned before end of two months.	
	{ 33 multiparae { 17 breast-fed. 16 weaned before end of two months.	
100 cases in houses	{ 21 primiparae { 11 breast-fed. 10 weaned before end of two months.	
	{ 79 multiparae { 50 breast-fed. 29 weaned before end of two months.	

In apartments the other residents object to a crying baby and worry the mother into bottle-feeding. Primiparae are easy to influence and have

not sufficient experience to resist the well-meant nagging of neighbours and relatives.

Summary

The case records kept at the Infant Welfare Centres in Liverpool were investigated for every fourth year over the period 1918-1937, and comparative tables and graphs were made in order to discover if there has been any decline in breast-feeding during that time.

The records of one of the health visitor's districts for 1937 for patients who did not attend the clinic were reviewed to determine the breast-feeding rate as compared with that of patients who attended the clinic. No appreciable difference was found.

One hundred family histories have been studied to discover if heredity influences breast-feeding, but no convincing evidence has been found to show that this is the case. On the other hand, there seems definite cause to believe that the influence of close relations and neighbours plays a considerable part in the maintenance of lactation.

The incidence of breast-feeding in mothers living in apartments has been compared with that among mothers occupying houses of their own. A further analysis of these cases shows that primiparae are much more easily influenced by neighbours and relations than are multiparae.

Conclusions

1. There does not appear to be any real decline in breast-feeding, but there is a shortening of the period of lactation.
2. There is no evidence that clinics cause a rise in the incidence of bottle-feeding.
3. The rate of breast-feeding is higher among women living in houses of their own than among those living in apartments. This is especially evident in primiparae.
4. The capacity for breast-feeding is apparently not hereditary. Parental influence, however, seems to play a part in the maintenance of lactation.

Thanks are due to Dr. W. M. Frazer, Medical Officer of Health for the City of Liverpool, to Dr. R. E. Bell, Senior Assistant Medical Officer in charge of Maternity and Child Welfare Department, for permission to examine the records, and to the health visitors for their kindness in collecting and sorting the case sheets.

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INGUINAL HERNIA IN FEMALE TWINS WITH SPECIAL REFERENCE TO THE IDENTIFICATION OF MONOZYGOTISM

BY

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It has long been common knowledge that certain twins resemble one another in a remarkable way. The fact that many more like sexed twins are born than the theoretical ratio 1 : 2 : 1 would demand constitutes evidence in favour of the belief that such twins are monozygotic, for the actual figures of twin births can be adequately explained on the assumption that about one half the pairs of like sexed twins are monozygotic. Granted, however, the existence of monozygotic twins their recognition is far harder than is generally realized.

If Pliny mentions how 'Toranius a merchant slave-seller, sold unto Marcus Antonius (now one of the great Triumvirs) two most beautiful and sweet-faced boies, for twins, so like they were to one another, albeit the one was born in Asia, and the other beyond the Alpes,' the lesson has been slowly learnt, and in 1930 Stocks stated that it was 'surprising to find with what assurance many writers on the question of twins regard their own ability to diagnose the monozygotic from the dizygotic with certainty, which can only be explained by the fact that no satisfactory check has so far been devised as to whether the diagnosis was right or wrong.' The method that Stocks proposed has in addition to its other virtues this, that it is sufficiently precise to admit of such checking. In elaborating this method Stocks has himself made use of two checks : all opposite sexed twins must be dizygotic ; the ratio of monozygotic to dizygotic twins as determined by his method should agree with that required on the general statistical grounds already referred to. He came to the conclusion that facial resemblance is not a reliable criterion of monozygosity, and believes that finger-print resemblances between corresponding fingers in twins furnishes the best means of separating monozygotic from dizygotic twins. This depends on the criterion that monozygotic twins have six or more patterns alike on corresponding fingers of the same-sided hands, whilst dizygotic have six or less alike ; in the ambiguous case when six are alike the diagnosis is completed by comparing the differences in height and four simple head measurements with tabulated values. His definition of alikeness is confessedly rather vague, and is that to a 'casual examination they should appear the same,' though this 'casual examination' implies an examination that only just falls short of counting the ridges, and a very close resemblance. Though this method is probably the most clear cut of any at the clinician's disposal it should be noted that it is not claimed that it will 'lead to a correct diagnosis in every case, but the errors will not be frequent enough to invalidate conclusions arrived at by using the methods in statistical researches on groups of twins,' and that furthermore the very phrase 'casual examination' introduces a subjective factor. Moreover,

this method did not actually completely satisfy Stock's own checks, since one, if not two, pairs of opposite sexed twins, and therefore certainly dizygotic, satisfied these criteria. He had on the other hand no means of showing whether monozygotic twins ever failed to satisfy them, and in this lies the chief interest of the following twins.

Case report

Annie and Isobella S. were brought to the Royal Victoria Infirmary, Newcastle-on-Tyne, in October 1936 because both of them had for the past two years symmetrical bilateral indirect inguinal herniae. They were just six years old, and country folk from the region of Berwick. Their mother was one of a family of seven; one of her sisters had had twin daughters, now aged twenty-two; apart from this she knew of no other twins in her family. So far as she knew there were no twins on her husband's side, nor did she know of any member of either side of the family having, or having had a rupture. Annie and Isobel were operated on by Mr. F. C. Pybus under whom they had been admitted on October 13, 1936; the diagnosis was in each case confirmed and a radical cure performed. As the photograph shows (fig. 1) the two children



FIG. 1.

resembled one another closely. Table 1 gives certain measurements and fig. 2 details of their finger-prints, slightly enlarged.

TABLE 1

MEASUREMENTS	ISOBEL	ANNIE
Head length	18.5 cm.	18.5 cm.
Head breadth	13.5 cm.	13.5 cm.
Circumference	53.0 cm.	53.0 cm.
Interpupillary distance..	4.75 cm.	4.75 cm.
Height	120.0 cm.	120.0 cm.
Weight	3 stone 11 lb.	3 stone 12 lb.

Discussion

Inguinal herniae are by no means rare; it is therefore rather remarkable that there should be so few cases on record of herniae in identical twins. De



FIG. 2.

Lange, who reported a case of bilateral inguinal hernia in a pair of male twins five and a half months old in 1936, could find in the literature reference to only one other similar case ; the case here recorded would appear to constitute the third. Whereas it is probable that many cases of hernia in twins are not reported because of their relatively unexciting nature, these figures certainly suggest that twinning in itself does not predispose to rupture. In the absence of any known external cause it seems reasonable to suppose that, as is generally held, the cause of these children's ruptures was congenital; it should then be possible, given adequate figures, to determine the likelihood that these twins are dizygotic and ruptured by 'coincidence,' thus determining their value as a check. The relatively simple nature of their affliction and its common occurrence encouraged

the belief that in this condition, if in no other, adequate figures would be forthcoming. In this we were to some extent disappointed, the best set of data being neither as modern nor as complete as might have been reasonably expected. None the less it is possible to make a rough estimate of the requisite probability, an estimate that may be expected to err on the right side. Such a statistical approach might have been vitiated had these children come of a stock peculiarly prone to rupture, or if there had been reason for supposing that twinning in itself was liable to lead to rupture ; the absence of any history of rupture in the family, together with the extremely few cases of rupture reported in twins appeared to dispose of these possible sources of error.

We have to estimate, supposing the twins dizygotic, the probability of the case being a 'coincidence,' i.e. the probability that the second child, who is (*a*) a dizygotic twin, and (*b*) also a female, should have developed, and be brought up for treatment for, a double inguinal hernia, between the ages of one and five.

The available statistical information is derived from the records of the London Truss Society as presented by J. Macready (1893), and from similar records made at the Bureau Central in Paris by P. Berger (1896). Unfortunately the two sets of statistics are seriously discordant in many respects. Berger has explained some of the discrepancies as due to differences in the manner of collection of the records, but it is difficult to trace the origin of the others. Another essential piece of information comes from the records of medical examinations of conscripts in Paris (Berger, 1896), which show that in the (census) year 1881 the proportion of conscripts judged unfit for full service on account of hernias was one in seventy-eight. Similar examinations in other places have given both higher and lower proportions than this. We shall, however, take this value, since for our purpose it would suffice to deal only with the more obvious cases of hernia.

We shall write :

h =number of females in age-group one to four brought to be treated for double inguinal hernia.

f =number of females in this age-group of the population,

H =number of men in age-group twenty to twenty-four presenting themselves to be treated for hernia,

P =proportion of males in this age-group rendered not wholly fit by hernia,

M =number of males in this age-group of the population,

p =proportion of females in age-group one to four requiring treatment for double inguinal hernia.

We have already seen that we may take $1/78$ as an estimate for P ; the numerical values of the other quantities can be supplied by Berger's or by Macready's statistics.

We seek first the proportion of people in the population unfitted by hernia that presented themselves for treatment (at the Truss Society or at the Bureau Central), supposing with Berger that this proportion is the same (at least approximately) for both sexes and all ages. The proportion can then be determined by considering men of the age-group twenty to twenty-four ; it is plainly H/MP . Therefore the number of females unfitted by hernia in the age-group

one to four of the population must equal hMP/H . Lastly, this number bears to the number f of females in this age-group the proportion $p=hMP/Hf$.

Using Berger's statistics * we have, in round figures, $h=4$, $f=75,000$, $H=200$, $P=1/78$, $M=147,000$.

These give for p the value $(4 \times 147,000)/(78 \times 200 \times 75,000) = 0.00050$, or, 1 in 2,000.

Using Macready's statistics † we find $h=18$, $f=1,377,000$, $H=975$, $M=1,115,000$, the population figures, which here refer to England and Wales, being taken from the Registrar-General's Report on the census of 1881. It is clear from the (less detailed) figures given for London that we shall commit at the worst an error of about 10 per cent. by using the figures for the whole country. We now get for p the estimate $(18 \times 1,115,000)/(78 \times 975 \times 1,377,000) = 0.00019$ or slightly less than 1 in 5,000.

Thus the estimates suggest that the chances are some thousands to one against the present case having arisen by coincidence. This suggests strongly indeed that these children are monozygotic, but as shown in fig. 2, not more than five pairs of their finger prints are similar; a view confirmed by Dr. P. Stocks (1938) himself, who, on that evidence alone, would have concluded that the probability of their 'being monozygotic was small though not zero.' He continues: 'I have met with a few twin pairs having only four or five similar prints who appeared from other physical resemblances to be monozygotic, and I think one can only say that in such cases the pair is much more likely to be dizygotic than monozygotic.'

In the present case we have seen that the chances of the twins resembling each other in having the type of hernia in question at about the same age 'by coincidence' are probably less than 1 in 1,000: whereas the chances of dizygotic female twins—or of any pair of sisters—having facial or other physical resemblances can hardly be of this order of smallness. Hence it seems safe to conclude that in this instance the clinical evidence outweighs the comparative lack of similarity in the finger prints, and that therefore, at least in exceptional cases, monozygotic twins may have not more than five pairs of finger prints 'similar.'

This pair, which may be compared with a known dizygotic like-sexed pair described elsewhere (Kellett, 1933), constitute then a helpful check on Stock's method, and we believe with him that 'it is only by the laborious collection of such cases that the real probabilities of different degrees of finger-print similarity can be assessed in the two varieties of twins.'

I am much indebted to Mr. F. C. Pybus, M.S., F.R.C.S., under whose care these twins have been, to Dr. H. P. Mulholland, M.A., Ph.D., of the Department of Mathematics, King's College, The University of Durham, who is responsible for the calculations of probability, and to Dr. Percy Stocks of the General Register Office, Somerset House, London, for all the help they have given me.

* *Loc. cit.*, pp. 77, 84, 85, and 103. The figures for M and f refer to the population in the Department of the Seine; the latter has been estimated on the basis of the figure given by Berger for Paris.

† *Loc. cit.*, pp. 6, 7, and 249. We have neglected some of the rare types mentioned elsewhere by the author. Moreover, h is estimated to be 18 on the basis of the author's figure for the age-group one to five.

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RENAL LESIONS IN CHILDREN WITH ERYTHEMA NODOSUM

BY

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Some years ago I had the opportunity of observing three children with erythema nodosum, in whom an acute haemorrhagic nephritis appeared simultaneously with the skin eruption. All three children were tuberculin sensitive, and in our opinion the tuberculous infection directly or indirectly played a part in the occurrence of the erythema nodosum. In one of the cases a pronounced primary pulmonary tuberculosis was present at the same time.

This simultaneous manifestation of erythema nodosum and haemorrhagic nephritis gave rise to a discussion as to the possibility of there being a connexion between these two manifestations of disease. We did not believe that one affection had produced the other, but took into account the possibility that both affections might be due to a common cause. In Scandinavia we consider erythema nodosum to be an allergic manifestation of disease, and haemorrhagic nephritis is by many workers also classed among the allergic phenomena. I shall not here enter into a discussion of this point of view.

Now haemorrhagic nephritis is the clinical manifestation of a series of renal changes, decreasing in intensity, in which there are subclinical transitions to normal conditions. Recent investigations have shown that some of the morphological elements occurring in a nephritic urine, especially red blood corpuscles and casts, may even normally be excreted in the urine. Quantitative tests by Addis's method have made it possible to fix the boundary-line between the physiological and pathological conditions in this respect.

Assuming that subclinical renal changes in erythema nodosum might be much more common than can be gathered from the limited number of clinically obvious cases of haemorrhagic nephritis (three cases of nephritis among more than eight hundred cases of erythema nodosum), the urine of eighty-eight children with erythema nodosum was examined by the Addis method. We considered, in order to be on the safe side, the upper normal limit of erythrocyte excretion to be at most 500,000 in twelve hours. The results are shown in the following tables :—

TABLE 1

No. of red blood corpuscles in thousands per 12 hours	NORMAL					PATHOLOGICAL							
	0-100	100-200	200-300	300-400	400-500		500-750	750-1000	1000-1500	1500-2000	2000-3000	3000-4000	>4000
Number of cases ..	23	15	12	8	6	Total 64	7	6	3	1	1	2	4 Total 24

TABLE 2

	NORMAL FINDING	PATHOLOGICAL FINDING
Tuberculin +	57	22
Tuberculin -	7	2
	64	24

From table 1 it will be seen that a pathological erythrocyturia was demonstrable in about every third or fourth child with erythema nodosum. After the disappearance of the erythema and the accompanying fever the urine finding again became normal. With regard to the examination carried out, special attention may be called to the following two points : (1) The renal lesions occurred also in children who did not display the least evidence of a complicating throat infection (table 3), and (2) they occurred just as often in the tuberculin negative as in the tuberculin positive cases (table 2). There is therefore no reason for assuming either that a tuberculous or that a streptococcal infection is a requisite condition for the occurrence of pathological erythrocyturia.

TABLE 3

	THROAT INFECTION DEMONSTRABLE	THROAT INFECTION NOT DEMONSTRABLE
Pathological erythrocyturia present	18	5
Pathological erythrocyturia absent	50	15
Total	68	20

At the same time as Addis counts, capillary fragility tests were made on the children's skin. These tests showed (table 4) that in children with erythema nodosum there is very often a capillary fragility, occasionally very marked, during the erythema nodosum fever. This capillary fragility occurred with

about the same frequency in children with pathological erythrocyturia as in those in whom this sign was not present. Nor was any relation shown to exist between the occurrence of simultaneous throat infection and the frequency and intensity of capillary fragility among the children with erythema nodosum.

TABLE 4

	CAPILLARY FRAGILITY TEST	
	POSITIVE	NEGATIVE
Pathological erythrocyturia present	7	13
Pathological erythrocyturia absent	18	27
Total . . .	25	40

Capillary fragility is by no means an unusual phenomenon in the majority of acute and chronic infections. It is thought to be due to a toxicologically-induced injury to the vascular endothelium. Since it can hardly be assumed that the capillary fragility demonstrated in the erythema nodosum cases depends on a local bacterial action of the agent that provoked the erythematous eruption, it must be concluded that in these cases, too, it is an expression of a toxic injury of the endothelium.

There is therefore good reason for also interpreting the erythrocyturia as an expression of a similar pathological change in the glomerular endothelium. The erythrocyturia in tuberculin positive cases of erythema nodosum is demonstrable only during the febrile stage of the erythema, during which stage the allergic sensitiveness to the tuberculotoxin is exceedingly great. It therefore seems very probable that the action of the toxin on the kidney is also greater during this period. Something similar occurs in all probability in the tuberculin negative cases of erythema nodosum, where the infection provoking the allergic-toxic syndrome erythema nodosum also produces capillary fragility of the skin and an endothelial injury to the glomerular endothelium.

Summary

During the toxic-allergic febrile state induced by various infections, during which erythema nodosum appears there is frequently present evidence of renal lesions, which are usually subclinical but may manifest themselves as an acute haemorrhagic nephritis. These renal lesions are probably to be regarded as an expression of the same toxic or allergic remote action of the infectious agent as that which produced the eruption of erythema nodosum and the capillary fragility of the skin.

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BRITISH PAEDIATRIC ASSOCIATION

PROCEEDINGS OF THE TWELFTH ANNUAL GENERAL MEETING

The Twelfth Annual General Meeting was held at the Old England Lake Hotel, Windermere, on Friday and Saturday, May 19 and 20, 1939.

FIRST SESSION (MAY 19, 10.0 A.M.)

Business Proceedings : The President, Dr. H. C. Cameron (London), was in the Chair, and there were present 55 members and 18 guests.

The Minutes of the last Meeting were read and approved.

The following Officers, and Honorary, Corresponding and Ordinary Members were elected :

President : 1939-40, Professor Charles McNeil (Edinburgh).

Secretary : Dr. A. G. Maitland-Jones (re-elected).

Treasurer : Dr. Donald Paterson (re-elected).

Representative for London : Dr. W. G. Wyllie, in place of Dr. W. P. H. Sheldon.

Representative for Ireland : Dr. W. R. F. Collis (Dublin), in place of Dr. Robert Marshall.

Honorary Members : Dr. J. Wilkie Scott (Past President), Dr. William Brown and Dr. R. C. Jewesbury.

Corresponding Members : Prof. Dr. Heinrich Finkelstein (Germany) and Dr. P. F. Armand-Delille (France).

Ordinary Member : Dr. R. E. Smith (Rugby).

The Treasurer's Report was received and adopted. It was decided to subscribe 10 guineas to the Society for the Protection of Science and Learning and 5 guineas to the Royal Medical Benevolent Fund.

The place of meeting for next year was then discussed.

Scientific Proceedings :

1. '*The results of Therapy in Childhood with Sulphanilamide and similar substances*'

PROFESSOR NOAH MORRIS (Glasgow) : The first sulphonamide to be introduced as a chemotherapeutic agent was sulphonamido-chrysoidine, commonly known in this country as prontosil rubrum. It arrived without any logical line of previous research, since the therapeutic properties of the sulphonamides had been quite unsuspected. The discovery that in the body prontosil was split up, yielding sulphanilamide, has led to a greater understanding of the action of the sulphonamides and to attempts to synthesize more powerful preparations. The sulphonamide group appears to be the essential fraction necessary for the chemotherapeutic activity of prontosil and its successors. Replacement of one H of this group has been attempted with the formation of two products that have attracted much attention, viz. sulfapyridine (M. & B. 693) and dimethyldisulphanilamide (uleron). The sulphonamides appear to have little action on either the cellular or humoral defence mechanisms of the host. At the moment there is evidence to indicate that the chief effect is to make conditions unfavourable for the invading organisms and so render them more susceptible to the defences of the host. This is probably achieved by preventing the organisms breaking down protein, so that unless nitrogenous foodstuff is present in a simpler form they are unable to obtain nitrogen. Possibly the bacteriostatic effect is due to the inactivation of some bacterial enzyme necessary for the utilization of food material. Sulphanilamide is readily absorbed and distributed through the body fluids. The concentration in these fluids is dependent upon dosage, rate and completeness of absorption, distribution ratio in the body and rate of excretion, which varies with renal efficiency and urinary volume. The best method of administration is by mouth, the parenteral routes being limited to patients in whom vomiting is a marked symptom.

DR. ALAN MONCRIEFF (London) spoke of the use of the sulphonamide preparations in streptococcal infections. He mentioned first the effects in tonsillitis, cervical adenitis and otitis media, for which good results were reported by most workers. Success was also claimed

in haemolytic streptococcal infections causing septicaemia, meningitis, erysipelas and impetigo, whilst in measles and pertussis evidence had been published strongly suggesting that septic complications were reduced by the use of sulphonamide drugs. As regards which preparation should be used the speaker suggested that in the absence of bacteriological certainty as to the presence of the haemolytic streptococcus 'M. & B. 693' covered a wider field than the original sulphanilamide group. Toxic effects were mostly absent in children. There was less agreement in the literature regarding the value of sulphonamide in certain other manifestations of streptococcal infection. In scarlet fever some workers held that septic complications were diminished, but others failed to confirm this. In rheumatic fever the evidence was emphatically against the use of sulphonamide in treatment, although some value in prophylaxis was suggested. Since toxic effects in rheumatic fever appeared to be increased it was suggested that similar harm might be done in nephritis. In view of these findings the possible dangers of the indiscriminate administration of sulphonamide in acute tonsillitis were briefly discussed.

PROFESSOR G. B. FLEMING (Glasgow) : The results of treatment of meningococcal meningitis and pyogenic infection of the urinary tract were discussed. It was shown that in thirty consecutive cases treated with serum, the mortality rate was 86 per cent. whilst in twenty-nine cases treated with sulphonamide (prontosil or M. & B. 693) it was 9·5 per cent. In the nineteen children who recovered there were no sequelae. Oral administration was usually effective, though in the early stages, when there was vomiting, intramuscular or intrathecal injections were thought to be of benefit. In view of the above results and those obtained by others, this form of treatment seems to be superior to any other. The results of treatment of pyogenic infection of the urinary tract with sulphanilamide were not so conclusive. Where there was no organic lesion the urine was sterilized in 73 per cent. of the cases, whilst in cases with a proved organic lesion it was sterilized in 43 per cent. These results are superior to those obtained by treatment with alkali and probably better than those treated with hexamine or mandelic acid. The drug acts best in *B. coli* infection. One of the advantages of treatment with sulphanilamide is that it acts in an alkaline medium and can be given in the acute stages of the disease.

DR. W. F. GAISFORD (Birmingham) : The difficulty of assessing the value of a new treatment for the pneumonias of childhood is great, because the mortality in lobar pneumonia is so low and in bronchopneumonia so variable. In 1936 the case mortality for lobar pneumonia under the age of fifteen at Dudley Road Hospital, Birmingham, was 3·8 per cent., and in 1937 less than 1 per cent. For bronchopneumonia the figures were 35 per cent. and 17 per cent. Since the introduction of '693' as a routine treatment 154 cases of lobar pneumonia and 178 of bronchopneumonia have been treated. There have been no deaths from lobar pneumonia and 15 from bronchopneumonia (8·4 per cent.). In the latter cases 93 per cent. were under the age of two years. As regards lobar pneumonia the chief feature has been the earlier fall in temperature. In 50 per cent. of the cases the fall occurred within twenty-four hours of admission and in 66 per cent. within forty-eight hours—as compared with 15·7 per cent. and 40·4 per cent. in the previous year—although the '693' treated cases were admitted on an average 1·75 days earlier than the 1937 cases. In the bronchopneumonias 52 per cent. fell within forty-eight hours. Clinical improvement occurred earlier, but no change was found in the rate of lung resolution. The incidence of empyema in the lobar pneumonias showed a slight increase, but the figures are too small yet to be of significance. Clear effusions, representing aborted empyemas, have certainly increased, and, although usually absorbed spontaneously, delayed convalescence. No serious toxic manifestations were encountered. The cause of failure in the bronchopneumonia cases was probably the mixed nature of the infecting organisms. In bronchopneumonia complicating whooping cough '693' had no constant effect. In severe cases parenteral administration of the sodium salt of '693' proved successful, but will be much less often called for than in adults, who so often vomit after the oral dosage. As regards dosage the essential part is to "saturate" the system as quickly as possible, giving large doses for the first eight or twelve hours. The accompanying table shows the suggested maximum doses for infants and young children.

TABLE OF MAXIMUM DOSAGE
Figures refer to tablets, not grammes. Each tablet = $\frac{1}{2}$ gramme

	INITIAL DOSE	TOTAL IN FIRST 12 HOURS GIVEN HOURLY, OR 2, 3, 4, OR 6 HOURLY	SUBSEQUENT DOSAGE 4 HOURLY
Weight 5 lb.	$\frac{1}{4}$	$\frac{1}{4}$
" 10 lb.	$\frac{1}{2}$	$\frac{1}{4}$
" 15 lb.	$\frac{3}{4}$	$\frac{1}{2}$
" 20 lb.	1	$\frac{1}{2}$
Age 2 yr.	2	$\frac{1}{2}$
" 3 yr.	2	1
" 4 yr.	2	1
" 5 yr.	3	1

The results to date, while not yet conclusive, are sufficiently encouraging to render continued use of '693' in the pneumonias of infancy and childhood justified.

2. FILMS were shown :

DR. G. BRAY (London) : 'The cutaneous manifestations of allergy.'

DR. R. COLLIS (Dublin) : 'Direct transfusion in infants, Soresi method.'

SECOND SESSION (MAY 20, 10.0 A.M.)

3. PROFESSOR A. WALLGREN (Gothenburg) : 'Renal lesions in erythema nodosum (see page 271).

4. PROFESSOR S. VAN CREVELD (Amsterdam) : 'Coronary thrombosis in young infants.' Two cases of coronary thrombosis in babies of seven and nine weeks were studied with Dr. F. H. ter Poorten. They gave rise to the questions : in how far does there exist a relation between a disease or an intoxication or a constitutional anomaly of the mother, and the occurrence of these peculiar deviations in the young infant ; and in how far these vascular changes play a rôle in the explanation of disturbances in respiration and circulation and in cases of sudden death occurring immediately or shortly after birth. In one case the mother for her bronchial asthma had during the whole pregnancy constantly used a prescription containing caffeine and lobeline. In the other case the mother also came from an allergic family and had ascaris-eggs in the stool. The first baby during four weeks before death suffered from attacks of dyspnoea ; clinical observation and the electrocardiogram pointed to the existence of myocarditis. The other baby died after a short illness consisting of attacks of cyanosis. In addition to the changes in the coronary vessels particular alterations were found in the kidneys : swelling of the capillary endothelium of glomeruli with local necrosis ; formation of peculiar crescents by the outer layer of Bowman's capsule. The hypothesis is assumed that the changes in the vessels are caused by the regular use by the allergic mother of drugs like caffeine with a localized effect or by the action of other toxins with an analogous reaction. Some experiments in favour of this hypothesis were mentioned.

5. DR. A. G. WATKINS (Cardiff) : 'Report on a recent polio-myelitis epidemic.' He reported an epidemic of thirty-three cases of polio-myelitis that had occurred in Cardiff from October to December 1938. The age incidence varied from six months to fifteen years, with twenty-three cases under five years old and eight cases under two. The mortality was twelve per cent. No two cases occurred in the same household, but the main incidence was in adjacent wards in the city. No cause of the epidemic had been found. Analysis of the signs and symptoms showed vomiting, fever, headache and limb pains to be the most frequent early symptoms, and four cases had scarlatiniform rashes. The various resultant paralyses were detailed and nine cases had a transient Babinski response which were not followed by any permanent upper motor lesion ; three cases had albuminuria and one had haematuria. Of thirty cases examined twelve had normal C.S.F., an increase in protein in twelve and an increased cell count in sixteen. Slides were shown of the nervous lesion in a fatal case, also of a liver showing toxic changes. Dr. Watkins expressed the view that in spite of experimental evidence, clinical manifestations such as albuminuria, rashes and toxic liver changes suggested a general systemic infection by the virus and not necessarily a pure neurotropic one.

6. DR. K. D. WILKINSON (Birmingham) : 'Salicylates and the myocardium.' Salicylates have been recognized for many years as specific remedies for the painful swollen joints, fever, and sweating of acute rheumatism, but there has been a tendency to deny that the myocardial damage which results from the rheumatic process can be modified by salicylates. Whatever may be the causal factor of acute rheumatism, there can be no doubt that the pathological process in the joints, pleura, arterial walls, and myocardium is of uniform type. A case of severe acute rheumatism with many swollen painful joints, fever, pericarditis, and evidence of myocardial damage—heart block—was treated with large doses of sodium salicylate (10 grains an hour) with twice as much sodium bicarbonate. Within three days the swelling and pain in the joints disappeared, the fever abated, and within ten days the pericarditis subsided. Within one month the obvious myocardial defects had cleared up and conduction was restored to normal. Daily electrocardiograms showed the gradual restoration.

7. DR. STANLEY GRAHAM (Glasgow). 'Epidemic enteritis of the newborn with unusual features.' The dangers of infection during the neo-natal period were commented upon. In 1938 an epidemic of enteritis occurred in a nursery for newborn infants at a large maternity hospital in Glasgow. There were eighteen cases in all, of whom ten died. Post-mortem examination was carried out in all the fatal cases, and the most outstanding feature was the high incidence of meningitis, no less than eight of the fatal cases showing a dirty, foul-smelling, purulent exudate over the meninges. In two cases there was a peritonitis and in two an acute inflammation of the gall bladder. *Bacillus enteritidis* (Gaertner) was isolated from the stools in every case, and from the meninges, peritoneum, and gall bladder in the cases showing

lesions in these areas. Such findings serve to illustrate the rapid invasion of the blood stream in cases of infection in the newborn infant. During 1938 there were 138 deaths out of 3000 live births in this Hospital. From autopsy records and other sources it was computed that of these deaths about 25 per cent. were associated with some infection.

8. DR. N. B. CAPON (Liverpool) : 'Observations on the paediatric section in the clinical reports of maternity hospitals.' After a reference to certain facts (e.g. infantile death-rate, neonatal death-rate, stillbirth-rate, etc.) given in the Annual Report of the Registrar-General for England and Wales, Dr. Capon suggested that a scheme might be drawn up for giving a standardized summary of the details recorded in the paediatric section of the medical reports of maternity hospitals, and of maternity departments in general hospitals. An arrangement of this sort would be complementary to the reports as they appear at present, and need not, therefore, interfere in any way with a hospital's present form of report. Paediatricians working with new-born babies would undoubtedly welcome the opportunity of having comparable statistics available, especially if these were made readily accessible by publication in one of the paediatric journals. Extracts from the paediatric section of the Liverpool Maternity Hospital Medical Report were shown to illustrate some of the points raised.

9. DR. R. E. STEEN (Dublin) : 'Some observations on tuberculosis in childhood.' Dr. Steen restricted his remarks to pulmonary tuberculosis in childhood. He first mentioned some types of adult phthisis met with in the child, and then described two cases of acute broncho-pneumonic phthisis in which the diagnosis had been made by demonstrating tubercle bacilli after lung puncture. He next mentioned chronic ulcerative and chronic fibroid phthisis, laying stress on the rareness of these forms of phthisis under the age of ten. He showed a film of a child of four years in whom the radiologist had reported cavities at an apex, but the case suggested a resolving apical pneumonia, the Mantoux reaction was negative in strengths of 1/1000, 1/100 and 1/10, and a few weeks later a further x-ray showed that the condition had entirely disappeared. He next showed slides of a case of chronic ulcerative phthisis in an older child, showing the active manner of spread at this age, and therefore the chance of adhesions being absent, good collapse having been obtained with pneumothorax in spite of the lung being riddled with cavities. The next case, also of chronic ulcerative phthisis in an older child, was described because though there were cavities at both apices and plenty of tubercle bacilli in the sputum, the sedimentation rate was normal on two occasions, being 2 and 5 respectively. He also mentioned a case of acute miliary tuberculosis in which the sedimentation rate had been 10, and asked if there could be any analogy between this and the fact that in terminal states the temperature also could fall to a normal level without indicating an improvement in the patient's condition. He then described some cases of primary infection in childhood, most of them being from families in which another child had died of tuberculous meningitis. In two cases 'contact' had not been with a relative, but a friend suffering from phthisis and expectorating tubercle bacilli. He then showed a series of films which appeared to show the evolution of tuberculous infection in childhood in all its three stages of primary, secondary and tertiary infection.

10. DR. R. S. ILLINGWORTH (London) (introduced by Dr. D. Paterson) : 'Acute focal and acute diffuse nephritis.' The criteria given by Volhard and Fahr for the distinction of focal from diffuse nephritis—the absence of oedema in the focal type, the absence of symptoms, of nitrogen retention, hypertension and oliguria, the occurrence of the nephritis at the height of the infection and the good prognosis, were mentioned and then applied singly and in combination to 301 cases of acute nephritis seen in the Hospital for Sick Children, Great Ormond Street, in the last eleven years. Taking oedema as the chief criterion, it was found that cases with oedema exhibited no difference in etiology, symptomatology, time interval between infection and nephritis, degree of nitrogen retention and prognosis from those without oedema. Cases satisfying two of the criteria for the diagnosis of focal nephritis—the absence both of oedema and of symptoms—were then discussed, and it was found that the majority of these showed nitrogen retention, and that on re-examination six years after the onset there was still evidence of renal damage. Five criteria were then applied in combination to the total of 301 cases, and it was found that only one case out of the entire series fulfilled these criteria. It was concluded that acute focal nephritis is not a clinical entity.

PROGNOSIS IN COELIAC DISEASE

A REVIEW OF SEVENTY-THREE CASES *

BY

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Information as to the prognosis in coeliac disease is not abundant. Several series of cases have been reported, but the mortality given varies considerably ; there are fewer records of the fate of those children who do not die of the disease.

Fifty years ago Gee (1888) wrote, 'death is a common end,' and Lehndorff and Mautner (1927) thought the prognosis was so hopeless that treatment was of little avail. Sauer (1927), however, recorded a series of twenty-five cases with one fatality. Evidence from another aspect was given by Bennett, Hunter and Vaughan (1932), who collected fifteen examples of the disease in adults, in most of whom the disorder dated from infancy. It would thus appear that though we may agree with Parsons (1932) and with Neale and others (1935) that coeliac disease responds remarkably well to treatment, yet there may be some cases that can run a protracted course. Such patients are not ill enough for their disorder to be recognized until adult age is reached, when, with the skeleton drained of calcium and crippled beyond repair, the disease declares itself. Facts in favour of this view will be given in this paper.

In the present investigation an attempt was made to learn the after-history of seventy-three cases of coeliac disease which had been in the Hospital for Sick Children, Great Ormond Street, London, between the years 1923 and 1938. The diagnosis of coeliac disease was made on the history of diarrhoea, anorexia and loss of weight, accompanied by the classical clinical features, and with the finding of an excess of normally split fat in the stools on more than one occasion. Only those patients have been included who were under observation long enough for an illness due to a transient digestive upset to be excluded.

Fifteen years have elapsed since the first patient was in the Hospital, and the oldest living subject is now sixteen-and-a-half years old. Twenty-two died in Hospital, and all but ten (fourteen per cent.) of the remainder have been

* Based on a Thesis submitted for the M.D. degree of the University of Cambridge. The work was done with the aid of a grant from the Medical Research Council.

traced. Those alive have been examined to determine if the disease was active, cured or quiescent, or if it had left any trace of its activity.

The cases

Age and sex incidence.—Of the seventy-three cases, forty-seven were girls and twenty-six were boys. This sex incidence agrees with that of all other published series in that the disease is almost twice as common in girls as in boys. The age of onset in those in whom it could be ascertained with any certainty is shown in the diagram (fig. 1). The age taken is that given by the parents as the date when symptoms were first noticed. Objection may be taken to

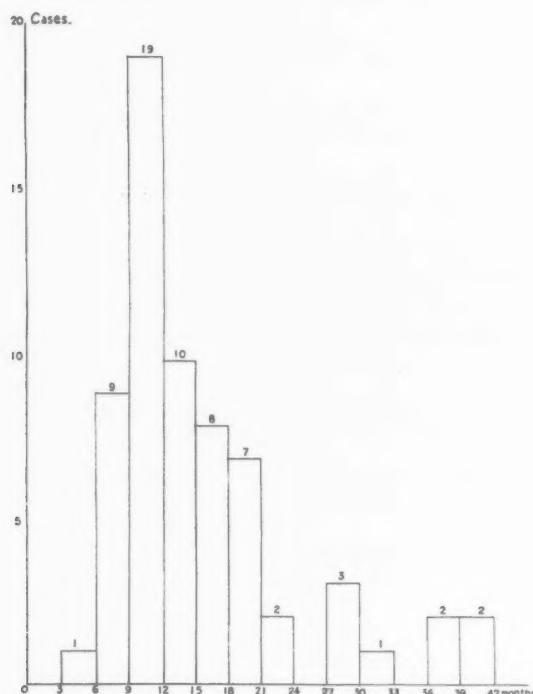


FIG. 1.—Diagram to show the approximate age at onset of the disease.

this as in some instances the onset of the disease may be dated from some minor gastro-intestinal upset unrelated to coeliac disease ; in others the disease may have been present for some time before it was noticed. But the figure shows that almost eighty per cent. of the cases occurred between six and twenty-one months ; this again is in agreement with most authors. There was no difference between the number of patients who were breast-fed and those who were bottle-fed ; but none of the very young ones was breast-fed.

General appearances.—The general appearance of the children varied with the severity of their disease and the stage in which they were seen. There is nothing to be added to the many admirable clinical descriptions which have already been given. The general wasting, with distension of the abdomen

and deflation of the buttocks is well seen in the photograph of five children who were in the wards at one time (fig. 2).



FIG. 2.—Photograph of five cases of coeliac disease showing the general clinical features.

Skin rashes.—Five cases had rashes, which are described as being purpuric in two cases, psoriaform in one, mottled in one and as a sweat rash in one.

Peristalsis.—This was seen in three cases. It is observed no doubt owing to the thin abdominal wall. But a knowledge of its occasional occurrence is not without importance in that one child was subjected to a laparotomy as a consequence of its appearance.

Ascites.—Only one patient showed this, but here again it should be remembered, as the child was operated upon as a case of tuberculous peritonitis.

Clubbing of the fingers.—This occurred in two girls; both these were older than the rest when they came under observation and the disease had been present for some time.

Laboratory investigations

All the patients were investigated in various ways in the laboratory. The results would, in some instances, appear to have an important bearing on the

prognosis of the disease. They are therefore discussed in some detail in the section which follows.

Fat metabolism.—Only those have been included in this series in which the stools showed the characteristic abnormality—namely an increase in the total amount of fat with normal splitting on more than one analysis. Transitory steatorrhoea can occur in any form of gastro-enteritis in infancy. The amount of the fat in the faeces is not necessarily an indication of the severity of the disease; there was no difference between the average highest faecal fats of those who died and those who recovered. The highest values in the series, 75·6 per cent. and 73·9 per cent., were, however, given by patients who subsequently died. In most instances the faecal fat should fall within normal limits when a low-fat diet is introduced. After this it bears a strict relationship to the fat-content of the diet and to the condition of the patient. Any increase in intake of fat before the patient can tolerate it leads to an excess of the faecal fat and there is a similar rise if the patient suffers a relapse (tables 1 and 2).

TABLE 1
EFFECT OF DIET ON FAECAL FAT PERCENTAGE (FEMALE PATIENT AGED 2½ YEARS)

	LOW FAT DIET	A LITTLE FAT	VERY LOW FAT DIET
Split	15·56	24·93	2·31
Unsplit	3·67	11·69	0·54
Total faecal fat ..	19·23	36·62	2·85

TABLE 2
EFFECT OF A RELAPSE ON THE FAECAL FAT PERCENTAGE (FEMALE PATIENT AGED 2½ YEARS)

DATE	JUNE 7	JUNE 19	JULY	AUG.	SEPT.	NOV.	JAN.
Condition ..	On ad-mission					Relapse	
Total faecal fat, per cent. ..	51·8	37·8	9·25	11·8	12·3	25·75	13·75

The response of the faecal fat to dietetic treatment is of some importance in estimating the prognosis of the disease. Of those who died, seven had three or more fat analyses done, and in five of these a normal result was not obtained, despite strict dieting.

Carbohydrate metabolism.—

ORAL GLUCOSE TOLERANCE CURVES. The characteristic oral glucose tolerance curve in coeliac disease is flat, that is a rise of less than forty milligrammes from the fasting value (Thaysen and Norgaard, 1929). Fourteen of the present series were investigated by this method. The curves are all abnormal

(fig. 3). Twelve of the curves are flat, the remaining two approach the normal, and both these patients were becoming convalescent. This has been shown by other workers (Thaysen and Norgaard, 1929; Macrae and Morris, 1931; Badenoch and Morris, 1936) and its value in prognosis is obvious (table 3).

TABLE 3

TO SHOW RETURN OF BLOOD SUGAR CURVE TO NORMAL AS RECOVERY TAKES PLACE (MALE PATIENT AGED 2½ YEARS)

	FASTING	½ HR.	1 HR.	1½ HR.	2 HR.
Nov., 1935 ..	81	70	85	85	87
Feb., 1936 ..	68	113	113	106	91
Mar., 1936 ..	46	39	59	72	95
Apr., 1936 ..	75	100	95	116	102
May, 1936 ..	79	88	90	80	76
Feb., 1937 ..	90	160	95	103	102

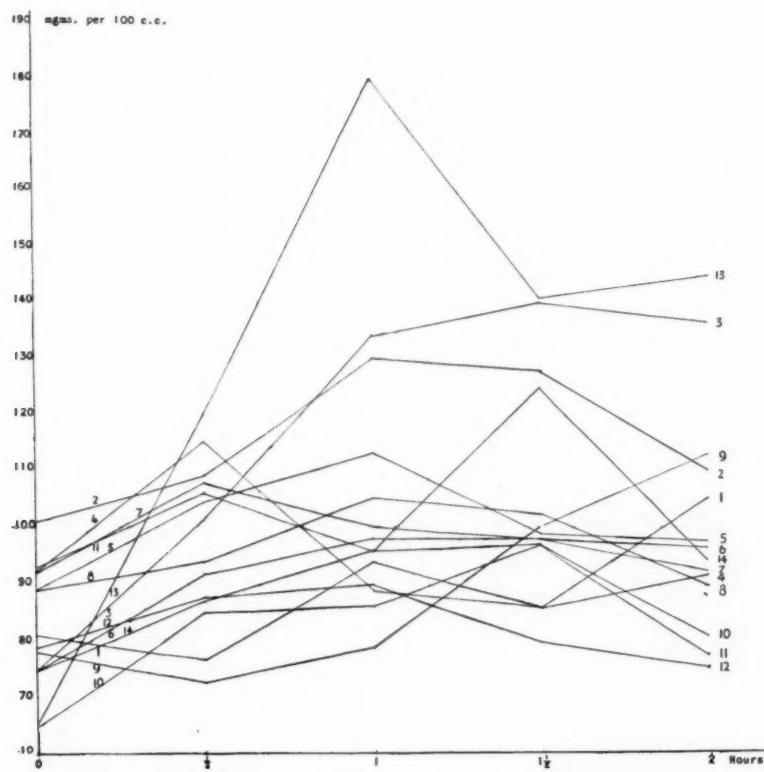


FIG. 3.—Glucose tolerance curves in fourteen cases of coeliac disease.

The curves obtained differ from those previously published in that the fasting values are not low. In each case there had been a period of fasting of not less than eight hours before the test. The dose of glucose given was one gramme per kilogramme body weight.

INTRAVENOUS GLUCOSE TOLERANCE CURVES. Recently attention has been directed to the value of intravenous glucose tolerance curves in coeliac disease.

So far published results show no agreement and the need for the standardization of technique is marked. Thaysen (1929a) obtained flat curves, whereas Ross (1936) showed curves in which the first values after the injection were high. Crawford (1938) stressed the importance of considering the length rather than the height of the curves, whilst most recently Ross (1938) has advocated the measurement of the area of the curves. None of the present series was investigated by this method.

Calcium, phosphorus and phosphatase.—Sixteen out of twenty-seven cases investigated had a serum calcium below 9 mgm. per 100 c.c. Five of these had tetany, the lowest value recorded being 3·9 mgm. per 100 c.c.; two of these died. Nineteen had the inorganic blood phosphorus estimated and in fifteen of them it was below 4 mgm. per 100 c.c. The normal phosphatase is taken as 10–20 units up to two years and from 5–15 units after this. The low blood phosphatase in coeliac disease has already been demonstrated by Morris and Peden (1937). In only six out of sixteen cases was the phosphatase above the lower level of normal, in the remaining ten being of the order of two, three or four units. The low values are evidence of the almost complete cessation of growth which occurs in coeliac disease. A rise in the phosphatase to within normal limits is not necessarily a sign of good prognosis. The highest value obtained was 53 units in a patient who was in a quiescent phase of the disease, but who had active rickets. The possibility of this happening in a patient who would otherwise appear to be improving should be remembered.

Fractional test meals.—Eleven cases were investigated by this test; all were deficient in secretion of hydrochloric acid and four of them showed achlorhydria. No histamine test meals were done.

Blood counts.—Of thirty-three who were investigated, twenty-nine patients showed some degree of anaemia. In twenty-one of these the colour-index was low; in the remaining eight the anaemia was orthochromic or hyperchromic. Unfortunately no measurements were made of cell size so that it is impossible to say if the macrocytic anaemia found in other series occurred. The hypochromic anaemia is due to iron deficiency and is aggravated by the restricted diet, by the absence or diminution of the gastric hydrochloric acid, and by deficient absorption owing to the diarrhoea. The degree of anaemia in an untreated case is thus proportional to the severity of the disease and is of corresponding significance in prognosis.

Radiology

Skiagrams of the bones were taken in sixteen of the patients. Seven of them were reported as normal. One patient showed active scurvy. Four showed general decalcification. Four showed active rickets, the youngest being an infant of seventeen months; two of these, aged four-and-a-half and eleven-and-a-half years, showed pathological fractures. The process of healing when calcium, vitamin D and ultra-violet light are given is shown in the photographs (fig. 4). The rapid appearance of the missing centres of ossification is striking.



No. 1.
Age 4 yr. 4 mth.



No. 2.
Age 4 yr. 8 mth.



No. 3.
Age 5 yr. 3 mth.



No. 4.
Age 5 yr. 11 mth.



No. 5.
Age 7 yr. 10 mth.

FIG. 4.—To show the healing which occurs when coeliac rickets is treated. Note the rapid appearance of the centres of ossification and the disappearance of the Harris's line.

Course and treatment

The chronic nature of coeliac disease, the periods of rapid improvement and equally rapid deterioration, for either of which no cause can be found, are well known. They were seen in many cases in the present series, and fig. 5

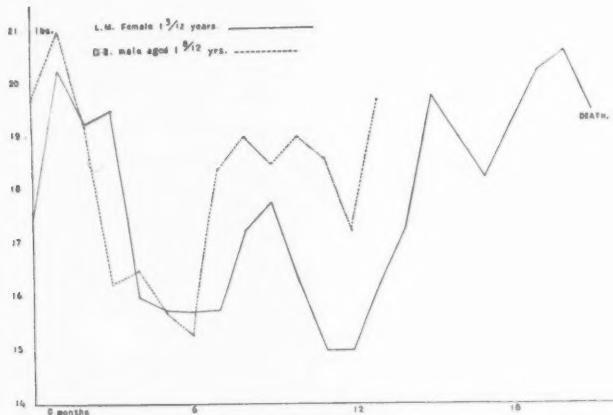


FIG. 5.—Weight charts of two cases of coeliac disease.

shows the weight chart of two patients over a long period. These 'natural' fluctuations of the disease must be borne in mind in estimating the value of treatment, and any new remedy must be used consistently over a series of cases before it can be accepted.

The children were kept in hospital long enough for the diagnosis to be confirmed and a satisfactory response to treatment to be obtained. When it was judged safe they were transferred to the country branch at Tadworth, Surrey, or to their homes and their supervision was continued as out-patients. The preliminary period of hospitalization varied from two to fifteen months, and on an average was five months. Including the time they spent at Tadworth they were under direct observation for much longer ; thus one boy spent five consecutive years either at the hospital or its branch.

The present series contains examples of practically every known form of therapy which has been suggested—bile salts, opium, insulin, pancreatic extracts, campolon and nicotinic acid were all included. The only common denominator in the treatment was a low-fat diet with added vitamins. This was given in some modification of the three-stage diet introduced by Howland (1921). Such a régime forms the best method of treatment, and has been universally recognized. The value of any other substance in the disease, whatever its claims theoretically or experimentally, has still to be proved.

Mortality

Twenty-two patients died during the period in the wards of the hospital or its country branch ; to these may be added four who died subsequently,

as far as can be ascertained of the disease, a total mortality of thirty-six per cent. Compared with other published figures this is high (table 4).

TABLE 4
MORTALITY IN COELIAC DISEASE
(Modified from Sauer, 1927)

NAME	DATE	NUMBER OF CASES	MORTALITY PER CENT.
Heubner ..	1909	10	10
Still ..	1918	41	14
Lichtenstein ..	1921	9	22
Howland ..	1921	30	0
Hablutzel-Weber ..	1923	26	23
Pipping ..	1924	6	50
Schaap ..	1926	114	11
Sauer ..	1927	25	4
Thayesen ..	1929b	23	22
Parsons ..	1932	94	10.6
Neale ..	1935	93	12
Hardwick ..	1939	73	36

In the four in whom death was not directly attributable to the disease, it was due to intussusception, measles, diphtheria and influenzal bronchopneumonia. Excluding these the mortality is thirty per cent. To some extent this high figure may be explained by the fact that the Hospital for Sick Children has a more than parochial reputation and not only do the patients come from a wide area, but also the more severe cases tend to gravitate there.

It is usually said that death in coeliac disease is due to an intercurrent infection, but in seventeen of the twenty-six fatal cases it was directly due to an exacerbation of the disease. The diarrhoea was increased, dehydration became intense, and the final picture was that of death from a severe enteritis. In only four did bronchopneumonia play a leading part.

Table 5, showing the age at which death occurred, emphasizes the danger of the disease in its early stages and the need for adequate treatment once it has been recognized :—

TABLE 5

YEARS ..	0-1	1-2	2-3	3-4	4-5	5-6	16-17
DEATHS ..	0	11	8	2	2	2	1

Results of the Investigation

A case of coeliac disease can only be said to have recovered when he passes normal motions on a normal diet and maintains this state. Remissions in the course of the disease are common, but in the present series no one who was

symptom-free for three years had a relapse. Of the original seventy-three cases twenty-two died in the hospital, leaving fifty-one to be accounted for. All but ten of these (fourteen per cent.) were traced. As has been said, four of them had died. Seventeen out of thirty-seven living patients who were traced appeared to have recovered. Their physical condition showed no signs of activity, they ate a normal diet and they passed normal motions and had been doing so for more than three years. A further ten were in a similar condition, but three years had not elapsed since the disease became inactive. Together these form a group of twenty-seven patients or thirty-seven per cent. of the whole. In six the disease is still active. Four have not yet become sufficiently well to leave the hospital or its country branch. Two are at home, but on a strict diet, any indiscretion causing a return of steatorrhoea.

Latent coeliac disease.—There remain four patients who have relapsed after having been well for as long as fifteen months, or who were thought to be well until analysis of their stools showed abnormal figures. To these the name latent coeliac disease is applied. This term was first used by Bennett, Hunter and Vaughan in describing fifteen cases of steatorrhoea in adults ; all except one of these gave a history of diarrhoea in childhood, had apparently enjoyed normal health for some time and had then presented themselves with advanced disease. Details of the four cases are given in the table, and the following is the history of one of them :

A.M., female, aged six years, was in the hospital from July, 1935, to January, 1937, with coeliac disease which had been present since she was eighteen months old. She was again seen in August, 1938, when her parents said she had quite recovered and was eating a normal diet and passing normal motions. She had grown, was no longer wasted (height 41½ in., weight 39½ lb.), the rickets which had been present was healed (see fig. 4), but an analysis of her faeces showed :

Split fat	30.10 per cent.
Unsplit fat	16.65 per cent.
Total fat	46.75 per cent.

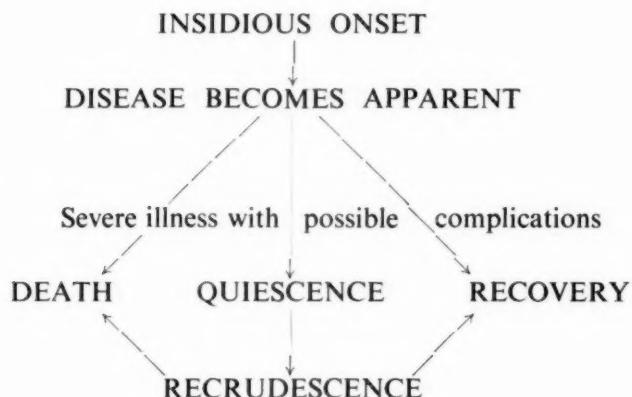
TABLE 6
LATENT COELIAC DISEASE

PATIENT AND SEX	AGE IN YEARS	TOTAL FAECAL FAT PER CENT.	REMARKS
E.B., Female ..	16	33.00	Undersized. Amenorrhoea.
A.M., Female ..	7½	46.75	Growing and gaining weight. Rickets healed.
O.W., Female ..	14½	30.27	Apparently in good health though undersized.
C.B., Female ..	5½	43.75	Relapse after 15 months. Flat glucose tolerance curves.

Parsons (1932) suggests that clinical recovery precedes biochemical recovery, meaning that the patient's physique is restored to normal before the fat-content of the stools. This condition cannot be regarded as a true recovery, but as a quiescent stage of the disease. Further evidence of the existence of such a condition may be adduced from a comparison of the frequency of the disease in children and in adults. The present seventy-three cases were collected over a period of fifteen years, yet in adults the condition is so uncommon that isolated examples are still being recorded (Mogensen, 1937 ; Riley, 1939). Though most patients probably recover or die there remain a few in whom the disease is long continued.

The absence of any story of diarrhoea when young in a case of adult steatorrhoea does not necessarily mean that the disease has arisen *de novo* and is not an example of latent coeliac disease. Such histories are based on the lay conception of diarrhoea and it is noteworthy that the parents of the patient A.M. above, strenuously denied that she had any abnormal motions, when actually she had copious steatorrhoea. Furthermore, Miller and Perkins (1923) have called attention to the occurrence of periods of apparent constipation in coeliac disease. Finally, skiagrams in long-continued cases show that the large bowel dilates, holding the bulky motions more easily, so that evacuation becomes less frequent.

The possible fate of a young child who develops coeliac disease may include years of illness and may be represented schematically thus :



Size of those followed up.—It is to be expected that such a severe and long-continued disease would leave lasting effects on the physique of the recovered patient. This has been shown to be so by other workers and Hablützel-Weber (1923) found forty per cent. of his living patients to be below the average physique. Schaap (1926), too, was of opinion that if the patient recovered he always bore traces of his illness, even when grown up. In the two diagrams the relation of the height and weight of thirty of the patients traced in relation to the average for their age is plotted. The six active patients have been excluded (figs. 6 and 7). Five of the patients were above the standard

height for their age. Three of these were over the standard weight, one was three-and-a-half pounds and one six-and-a-half pounds below the standard. Fifteen patients were more than two inches under height and five pounds under weight. Eight of these were more than ten, and four more than thirty pounds under weight. Two patients were within one inch in height, but more than ten pounds below weight. Six patients approximated to both standard height or weight.

Two patients were under height, but were five or more pounds over weight.

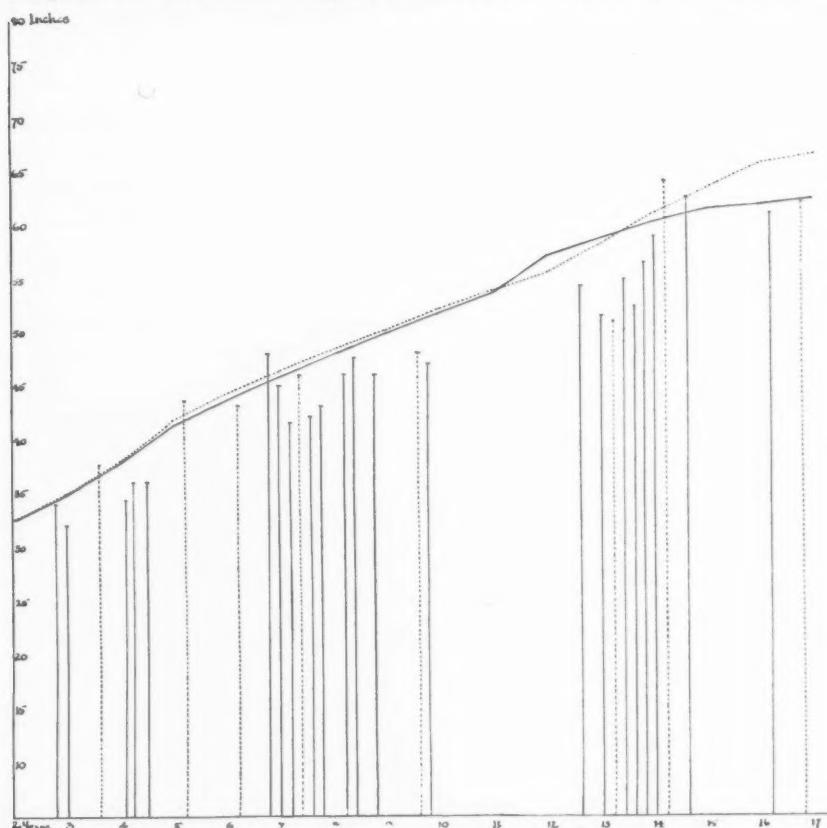


FIG. 6.—Diagram to show the height of those followed up compared with the standard for their age (Holt). Boys —— Girls -----

These patients thus appeared excessively fat, and this tendency for them to gain too much weight and so have the appearance of Fröhlich's syndrome has been thought by Parsons to be further evidence of the instability of their fat regulating mechanism. It is well shown in the photograph of a patient who subsequently died from influenzal bronchopneumonia (fig. 8). Eventually the condition rights itself as is shown by a boy who now, at the age of fourteen, is above both the standard height and weight ; a photograph of him at the age of six-and-a-half is most suggestive of Fröhlich's syndrome.

The imprint of coeliac disease is thus heavily written upon the stature of the child. As time goes on, and particularly as puberty is passed, this may get fainter, but in most cases it is probable that permanent record is left.

Haematology.—Blood counts upon those followed up showed only four with haemoglobin levels below 70 per cent. The anaemia was of a low colour index type and only one of them had steatorrhoea indicative of activity. Eight had haemoglobin values between 70 per cent. and 75 per cent., four between 75 per cent. and 80 per cent. and eight were over 80 per cent. No hyperchromic anaemias were discovered, thirteen patients had a colour-index between 0·9 and 1·1 and the remainder a low colour-index anaemia.

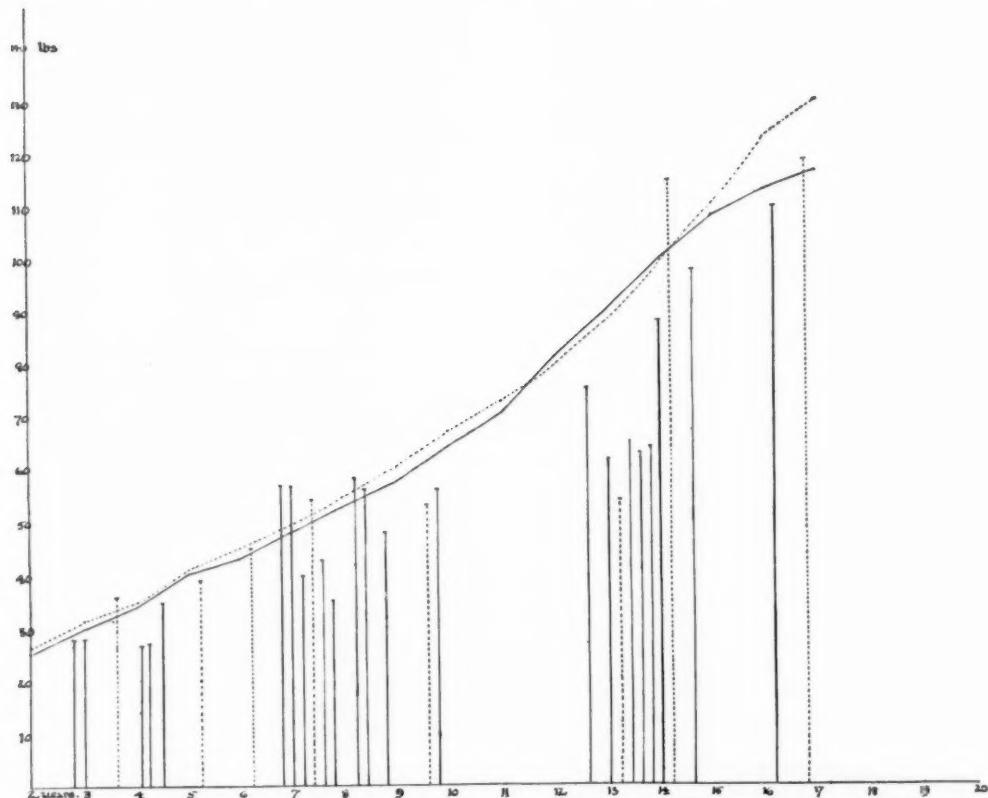


FIG. 7.—Diagram to show the weight of those followed up compared with the standard for their age (Holt). Boys ----- Girls —————

Other features.—**TEETH** : It might be thought that the teeth would show evidence of a disease which has such a profound influence on the metabolism of calcium. Unexpectedly most of the patients had good teeth ; there was only one with gross caries and one other with a mild degree.

MENTALITY : There appeared to be no serious retarding of the mentality of the patients. Those who had missed many terms at school would have compared badly with their more fortunate fellows, but this was due to lack of education and not of capacity to learn. This is in keeping with the behaviour of the children when they are in the acute phases of the disease and their precocity is so well marked.



No. 1.



No. 2.

FIG. 8.—Two photographs of the patient T. M. age 15 mth., and 5 yr. 4 mth. Note the tendency to obesity which may occur when recovery from coeliac disease takes place.

Summary

(1) Seventy-three cases of coeliac disease who had been patients at the Hospital for Sick Children, Great Ormond Street, London, for more than two months between 1925 and 1938 have been analysed and followed up, all but fourteen per cent. of the living patients having been traced.

(2) Twenty-six patients died. Excluding four who died when the disease was not active, the mortality was thirty per cent. This is high when compared with other series.

(3) Death was usually due to an exacerbation of the disease, the diarrhoea increasing and dehydration and intoxication becoming marked. Only four children died from bronchopneumonia.

(4) Seventeen patients appeared to have recovered clinically and biochemically for more than three years, ten had been in a similar condition for less than three years. Together these form a group of thirty-seven per cent. of the whole.

(5) Six patients are still in the first phase of activity of the disease.

(6) Four patients were thought to be well until stool analyses showed steatorrhoea. These patients are in a quiescent phase of the disease, which, if in adult life it becomes reactivated, is usually diagnosed as idiopathic steatorrhoea. To such the name latent coeliac disease should be given.

(7) Patients who have had coeliac disease tend to remain dwarfed, but their intellect is not affected and their teeth remain good. Anaemia does not as a rule persist.

Thanks are due to the Honorary Staff of the Hospital for Sick Children, Great Ormond Street, for providing access to the notes of these patients and allowing them to be investigated, to Dr. D. N. Nabarro, late Director of the Pathological Laboratory, for facilities to work in the laboratories, to Dr. Bertram Shires for permission to reproduce the skiagrams and to Mr. Deryck Martin for taking the photographs.

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THE USE OF IRRADIATED EVAPORATED MILK IN INFANT FEEDING

BY

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Although the incidence of rickets in England has been greatly reduced in recent years, mild cases are still seen too frequently even amongst infants attending infant welfare centres. This may be due either to the mother's failure to give the additional vitamin D that has been prescribed, or to insufficient amounts of vitamin D having been prescribed. If therefore any form of 'fortified' vitamin D milk were available at an economic price which could safely be relied on to prevent infantile rickets in artificially fed babies and could be given over long periods without ill effect, it would clearly have a valuable place in infant feeding. During the past fifteen years several types of fortified milk have been produced, though not all on a commercial basis. Examples are milk from cows fed with irradiated yeast, milk from irradiated cows, liquid and dried milk to which vitamin D concentrate has been added, and liquid, evaporated and dried milk which has been subjected to direct irradiation. Their relative values have been reviewed by Jeans (1936), who stresses the difficulties of comparing animal and human reactions to vitamin D and of accurate control of human experiments. A further source of error lies in the different methods of assay used by different workers. It is proposed here to consider only irradiated evaporated milk in relation to the prophylaxis and cure of infantile rickets.

After the discovery that the vitamin D content of foodstuffs could be greatly increased by exposure to ultra-violet light (Steenbock and Black, 1924; Hess and Weinstock, 1924), Steenbock and Daniells (1925) applied the principle to liquid milk. In succeeding years many experimental and clinical studies have appeared in the American and German literature with regard to the antirachitic properties of irradiated milk. Although the first clinical application was made by Cowell (1925) in England, and subsequent reports (Watson, Finlay and King, 1929; Nabarro and Hickman, 1929) have been favourable, the use of irradiated milk for infant feeding has attracted relatively little attention in this country.

At the present time three firms are producing irradiated evaporated milk in the British Isles on a commercial basis, and though none of them has put

forward any extravagant claims for the value of irradiation, it seems highly desirable that information should be available with regard to the reliability or otherwise of these products in the prevention of rickets.

Present investigation

In order to assess the prophylactic value of the milk, a group of normal infants was observed over periods of from three to six months, between October and April, during which time the irradiated milk served as the sole source of oral vitamin D. It was not, of course, possible to exclude all exposure to sunlight during the period of study, since the infants were being treated in their homes, but as all were living in London and the period of observation was limited to the six darker months of the year, it was felt that the conditions would provide a sufficiently severe test of a normal full-term infant's requirements. The more rigorous criteria recommended by Eliot and Powers (1935), by which both prematures and deeply pigmented infants are included in the group studied, were not fulfilled, since it was felt that the diet must first be shown to be sufficient in vitamin content for the normal infant before extending its use to those in whom the requirements will be greater.

The curative properties of the milk were tested in seven infants suffering from active rickets. Six of these patients were kept in hospital throughout the whole period of study.

Milk.—The brand of milk used in this investigation was a commercial preparation sold under the name of Irradiated Carnation Milk, an unsweetened evaporated milk having a caloric value of 53 per fluid ounce; one part of evaporated milk to one-and-a-half parts of water represents reconstituted cow's milk. The manufacturer's assays showed an average of 165 international units of vitamin D per reconstituted quart (40 fluid ounces). It should be emphasized, however, that the present study was not concerned with the per unit protective value of evaporated milk (in which case confirmatory assays of every batch of milk would be necessary, owing to the known difficulties of exact and permanent standardization of the irradiation process), but with determining if the milk as marketed did in fact have an appreciable antirachitic value and if so whether or not it was an adequate protection against rickets when given as the sole source of vitamin D in the diet, and used over a considerable period.

The manufacture includes evaporation at 135° F., homogenization and irradiation by the Steenbock process, using the carbon-arc lamp. In practice it was found that the milk was in fact successfully homogenized, there being little or no separation of the fat on standing, and that no unpleasant taste had been given to the milk (as is liable to occur with more prolonged irradiation).

It is not proposed to discuss the merits of evaporation of milk as such for infant feeding, since it is generally agreed that a reliable unsweetened evaporated milk provides a satisfactory basis for infants' formulas, that it has the advantage of being a clean milk which can safely be kept in the unopened tin, and that the evaporation process probably renders the curd more readily digestible than that of fresh cow's milk.

Normal group (prophylaxis)

Twenty normal full-term infants, who had received no previous antirachitic treatment, were examined clinically and radiologically for evidence of rickets, and in the absence of this were given irradiated evaporated milk in formulas appropriate for their age, the younger infants receiving not more than one-third of the total calories of the feed as added carbohydrate. They were in addition given orange juice and after the age of six months crusts and cereal; subsequently minced lean meat and potato were added.

The ages at the onset of treatment varied from six weeks to ten months, fourteen of the infants being under six months of age. Twelve of the infants, attending the Barley Mow welfare centre, lived in a poor district in North Lambeth ; the remaining eight all lived in London, but were on the whole from rather better homes. At the end of three months' treatment, the infants were re-examined clinically and radiologically for evidence of rickets, and again at the end of treatment if this fell within the experimental period (October to April). With one exception (a female infant who weighed 17 lb. at one year, after four months' treatment), the infants gained well on the irradiated milk and took it without difficulty after the first few days. Comparison with a control group of artificially fed infants receiving corresponding cow's milk or dried milk formulas with the addition of six drachms of cod-liver oil emulsion (50 per cent. cod-liver oil) daily showed no significant differences in weight increment or incidence of infection. The groups are, however, too small for emphasis to be placed on this. Although the original number of babies given irradiated milk was considerably more than twenty, there was no case in which the mother defaulted owing to dissatisfaction with the feeding.

Results.—Of the twenty patients, one showed evidence of mild active rickets both radiologically and clinically (beading and flaring of ribs and slight bowing of tibiae) after three months' treatment ; this infant was five months old when treatment was started. Two infants showed radiological evidence of healed rickets after three months. These were aged seven weeks and three months respectively at the beginning of treatment. As the original x-rays in all cases had shown no signs of disease, this suggests that both had developed slight rickets during the earlier period of treatment, the condition then healing spontaneously. Four patients showed clinical signs suggesting rickets (bossing of skull, widely patent fontanelle, delayed dentition, and beading of ribs) after three to six months' treatment, but no radiological changes. Several authors (Hess and Lewis, 1933 ; Davidson et al., 1937) have commented on this discrepancy between clinical and radiological evidence of rickets, and many are inclined to regard radiology as the final test. Indeed, 'antirachitic beading' of the ribs has been attributed to an excess of vitamin D. The remaining patients in this series appeared normal.

In addition to the experimental period, several patients were kept for considerably longer periods on irradiated milk (in five cases for as long as eighteen months to two years). In none of these were ill effects attributable to excess of irradiated milk observed. From the extensive experience of its

use by American observers it appears improbable that the pathological changes described in animals following excessive irradiation are at all likely to occur in human infants taking the commercial preparations of irradiated milk at present available (Hess and Lewis, 1932).

Rachitic group (curative properties)

Seven infants suffering from active rickets who had had no previous anti-rachitic therapy, were treated in hospital on a diet in which the irradiated milk provided practically the sole source of vitamin D. They were kept in the ward throughout the whole period of treatment, without exposure to ultraviolet light, with the exception of case 7, who was treated for two weeks (during November) in the home conditions in which the rickets had developed. In addition to the irradiated milk the diet consisted of orange juice (or fresh orange), cereal or porridge, bread, sugar and small amounts of lean beef or mutton and potato. The milk was given by cup as full-strength reconstituted milk, and in the concentrated form spread on bread or poured over the cereal or orange. In every case, the infants had been described by the parents as 'not liking milk' or difficult to feed, and most of them took one to two weeks to become used to taking more than eight to ten ounces of reconstituted milk in the day. After this time their average intake was in each case from twenty to twenty-five ounces a day, though considerable daily variation occurred.

Table 1 gives a summary of the cases. It will be seen that one infant was eight months old on admission, five were between one and two years old, and one was aged two years and four months. All came from very poor homes, the father being unemployed in six out of the seven cases. It is highly probable that the previous diet was deficient in calcium as well as vitamin D, at least in the case of the older children, and this should be borne in mind in assessing the response to treatment.

Biochemical investigations.—Serial estimations were made of serum calcium, plasma inorganic phosphorus and phosphatase during treatment in four cases (table 2). Case 1 showed a fall in phosphatase from 139 units before treatment to 14·1 after nine weeks' treatment, the calcium-phosphorus product rising from 26·4 to 57·8 over the same period (see fig. 1). Case 2 showed a somewhat anomalous initial value for the calcium-phosphorus product (50·9), falling to 36 after one week's treatment and subsequently rising to 50·7 after five weeks' treatment. The phosphatase was little raised at onset (25 units), falling to 15·2. In case 3 the calcium-phosphorus product rose in six weeks from 37·2 to 44·7, and the phosphatase fell from 45 to 16·9 units. The estimations on case 7 were begun after the infant had received irradiated milk for two weeks; the calcium-phosphorus product rose from 31·2 to 38·8 and the phosphatase fell from 26 to 10 units after a further three weeks' treatment. The biochemical findings therefore generally confirm the progress of healing under treatment with irradiated milk observed in the x-rays (see below).

Radiological investigations and results.—In each case, x-rays showed evidence of active rickets before treatment, though in case 4 (fig. 5) there was

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TABLE I

CASE	SEX	AGE (MONTHS)	ADMITTED	DISCHARGED	PRESENTING SYMPTOMS	BOSSING	ANTERIOR FON-TANELLE (FINGERS-BREADTHS)	BEADING OF RIBS	HARRISON'S SULCUS	BOWING OF LEGS	EPiphyseal ENLARGEMENT	WEIGHT (LB.)	REMARKS (FAMILY CONDITIONS: PREVIOUS FEEDING)	
												ADMISSION	DISCHARGE	
1. B. D.	F	28	28.iii.39.	9.vi.39.	Failure to walk	Present	Closed	Absent	Severe	Present	24½	26½	11 children. Diluted cow's milk from birth.	
2. B. P.	M	13	8.v.39	9.vi.39	Failure to walk	Absent	1	Present	Absent	Absent	21½	21	7 children. Father unemployed. Diluted cow's milk from birth.	
3. R. W.	M	8	4.v.39	9.vi.39	Head-sweating	Present	4	Present	Absent	Present	18½	19½	6 children. Father unemployed. Breast-fed to 8 months.	
4. P. J.	F	17	12.iv.39	5.vi.39	Bowing of legs	Absent	2	Present	Absent	Severe	Present	20½	22	12 children. Father unemployed. Diluted cow's milk from age of 1 month.
5. I. G.	F	21	25.iii.38	17.iv.38	Defective gait	Absent	Closed	Present	Severe	Present	23	23	7 children. Breast fed to 9 months.	
6. A. R.	M	17	2.ii.38	12.iii.38	Bowing of legs	Absent	1	Present	Present	Severe	Present	20½	22½	10 children. Father unemployed. 8 living in two rooms. Breast-fed to 16 months.
7. A. W.	M	16	8.xi.38	10.xii.38	'Going off legs'	Present	4	Absent	Absent	Present	Absent	21½	22½	Only child. Father unemployed. Treated with irradiated milk for two weeks before admission.

TABLE 2

CASE	DATE	SERUM CALCIUM (MGM. PER 100 C.C.)	PLASMA INORGANIC PHOSPHORUS (MGM. PER 100 C.C.)	Ca X P PRODUCT	PHOSPHATASE (UNITS)
1 B.D.	29.iii.39	8.8	3.0	26.4	139.0
	19.iv.39	9.0	3.3	29.7	59.7
	21.iv.39	—	—	—	50.0
	26.iv.39	9.4	4.7	44.2	51.8
	5.v.39	9.6	4.9	47.0	38.0
	11.v.39	9.4	5.2	48.9	32.0
	18.v.39	9.6	6.0	57.6	17.6
	26.v.39	9.6	5.2	49.9	11.8
	31.v.39	11.8	4.9	57.8	14.1
2 B.P.	11.v.39	10.4	4.9	50.9	25.0
	18.v.39	10.0	3.6	36.0	21.9
	26.v.39	9.8	3.9	38.2	16.4
	13.vi.39	10.8	4.7	50.8	15.2
3 R.W.	4.v.39	9.3	4.0	37.2	45.0
	11.v.39	9.0	4.6	41.4	14.1
	18.v.39	10.2	4.2	42.8	20.3
	26.v.39	9.5	4.4	41.8	16.1
	31.v.39	9.3	4.2	39.1	25.6
	13.vi.39	10.4	4.3	44.7	16.9
7 A.W.	9.xi.38*	7.8	4.0	31.2	26.0
	22.xi.38	8.1	3.9	31.6	16.0
	6.xii.38	9.7	4.0	38.8	10.0

* After two weeks' treatment.

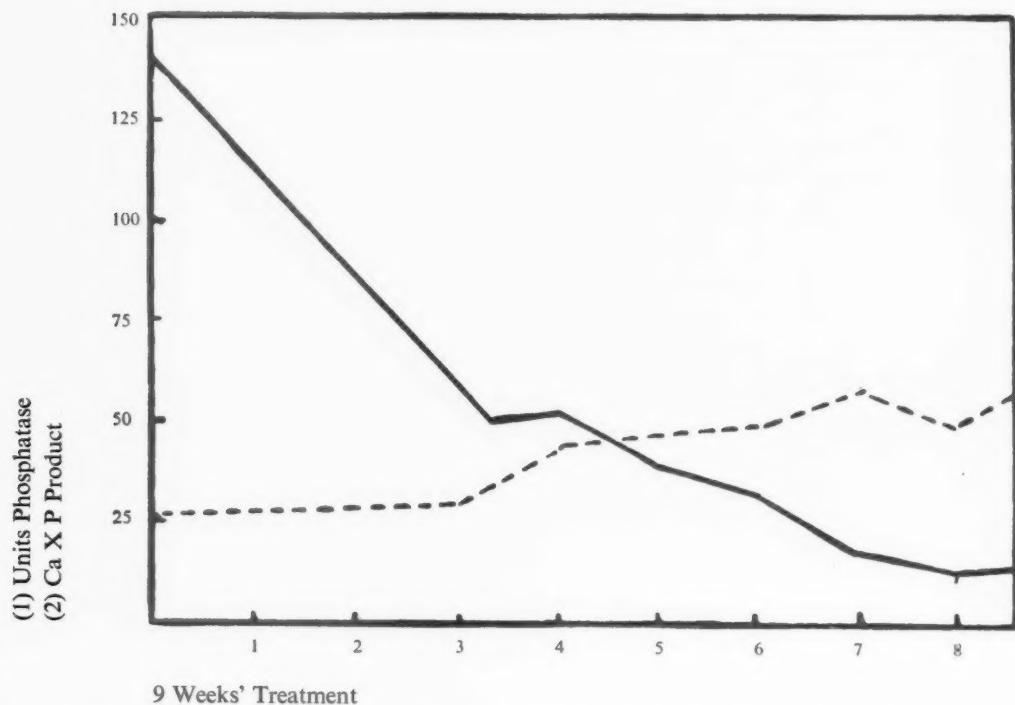


FIG. 1.—Showing effect of treatment on phosphatase (unbroken line) and on calcium—phosphorus product (broken line).

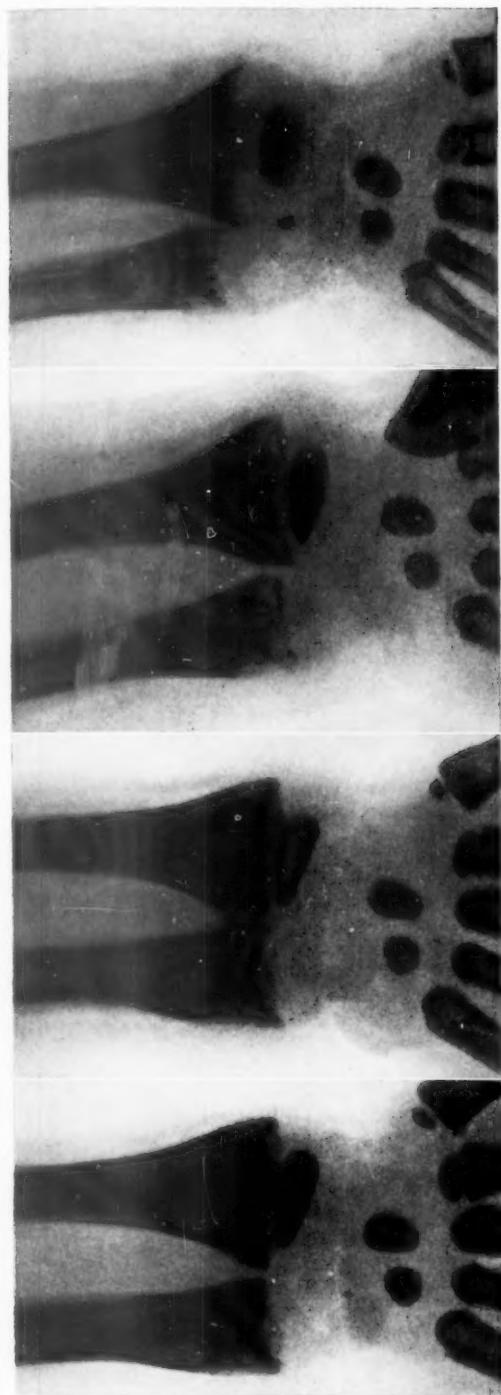


FIG. 2.—Case 1, B. D.
I : March 29, 1939. II : April 19, 1939. III : April 26,
1939. IV : May 11, 1939.

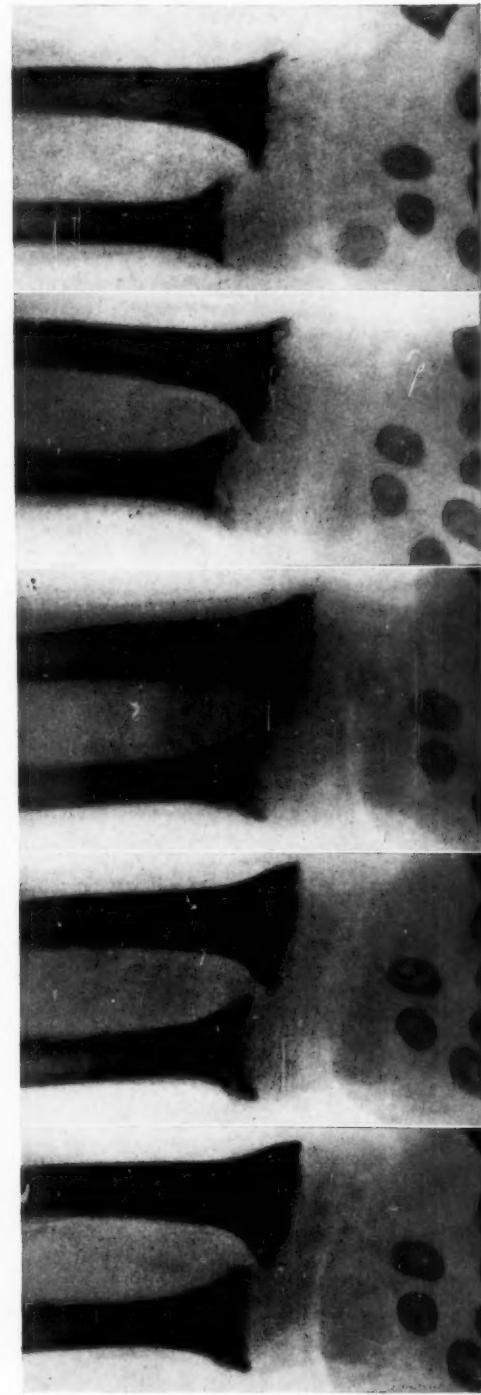


FIG. 3.—Case 2, B. P.
I : May 8, 1939. II : May 15, 1939. III : May 22,
1939. IV : May 30, 1939. V : June 5, 1939.

some slight coincident calcification present at the metaphysis of the wrist. Serial x-rays of the right wrist of cases 1 to 6 are illustrated in fig. 2 to 7. Case 7 showed less marked cupping than the other cases, but mild active rickets before treatment was started, and increased regularity of the metaphyseal line and calcification in four weeks. After treatment with irradiated milk, every

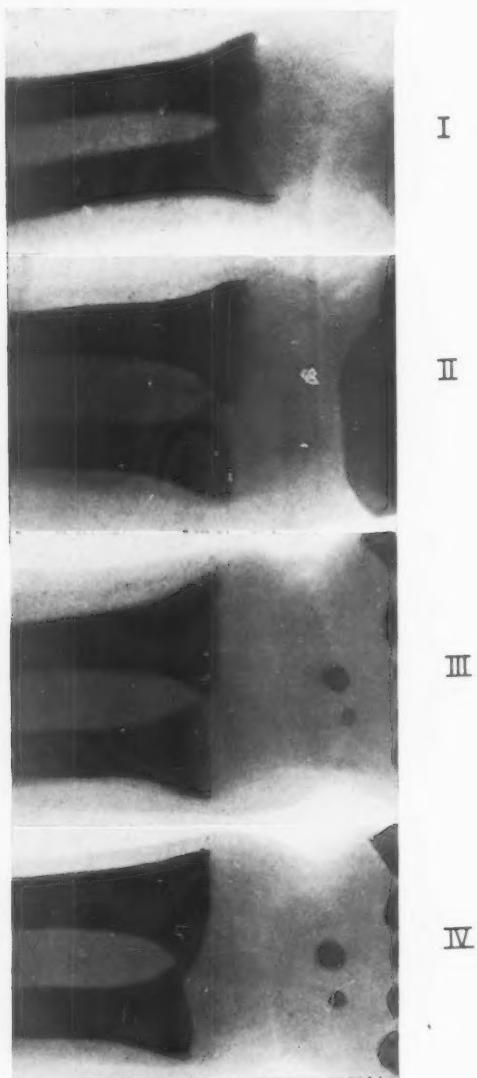


FIG. 4.—Case 3. R. W.
I : April 28, 1939. II : May 5, 1939. III : May 15, 1939. IV : June 5, 1939.

case shows clear evidence of progressive healing. This became recognizable in from one to three weeks, and in all cases had become well advanced in four to five weeks. The impression was gained, however, from case 1, which was kept under observation for a period of ten weeks, that there was little progress in the healing process after about six weeks, and that at the end of



FIG. 5.—Case 4. P. J.

I : April 12, 1939. II : April 21, 1939.
III : May 3, 1939. IV : May 17, 1939.

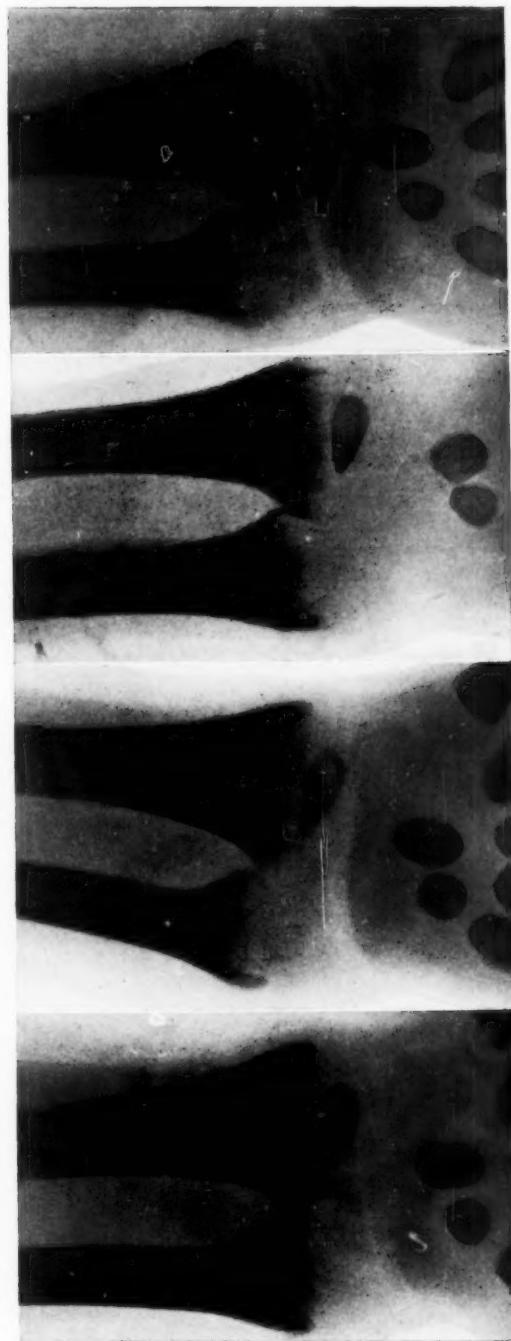


FIG. 6.—Case 5. I. G.

I : March 25, 1938. II : April 1, 1938. III : April 8, 1938. IV : April 30, 1938.

the period of observation calcification was less perfect than in a control case of the same age treated with 15 minimis of adexolin daily, ultraviolet light and a more normal diet. It is clear, therefore, that in this group of older infants suffering from active rickets, treatment with irradiated evaporated milk without other source of vitamin D was sufficient to initiate healing which was progressive

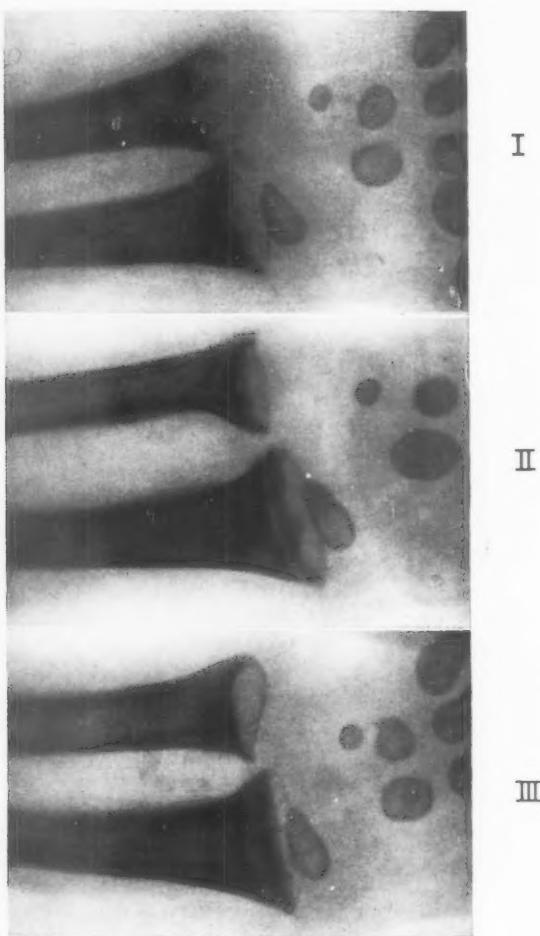


FIG. 7.—Case 6. A. R.

I : February 3, 1938. II : February 28, 1938. III : March 10, 1938.

for at least four to five weeks. It is not, of course, suggested that this method of treatment alone provides either the most rapid or perfect means of cure.

Discussion

The results obtained in the normal group of infants treated as out-patients during the winter and spring indicate that whilst irradiated evaporated milk of this potency may serve as a prophylactic against rickets in the majority of cases, it is not completely reliable for this purpose and that mild rickets may develop during its administration. Study of the rachitic group, on the other

hand, showed that its anti-rachitic properties were sufficient to initiate healing in every case. The apparent anomaly that the milk was sufficient to cure but not to prevent rickets is probably largely explicable by the age of the patients in the two groups. Thus in the case of the older rachitic infants, it was (after the first few days) possible to administer a larger total quantity of milk than to the younger infants, whilst the vitamin D requirements are relatively greater during the period of rapid growth in the first year than subsequently. It has also been shown experimentally, however (Bethke, Kennard, and Sassaman, 1927), that amounts of vitamin D insufficient for the prophylaxis of rickets in rats may produce some degree of calcification in rachitic rats on the same diet. There is known to be a considerable individual variation in the tendency to develop rickets, even in cases in which the experimental conditions can be controlled much more strictly than is possible in an out-patient study. The fact that a small percentage of these cases developed rickets whilst the majority remained free is therefore not surprising. It does, however, suggest that in the rickets-free patients the dosage of vitamin D approached the lower limit of safe protection. Jeans and Stearns (1934) have shown that whilst such a dosage may prevent manifest rickets, it may still fall short of the optimum for requirements for growth and calcification.

Although prematures were not included in the present study, Davidson et al. (1937) and others have shown conclusively that prematures are in much greater danger of developing rickets on irradiated evaporated milk than are full-term babies. This is due both to their more rapid growth and to the smaller total quantity of milk they are able to consume daily, although the number of units of vitamin D per kilogramme body-weight may be practically the same as that of full-term infants.

Summary and Conclusions

(1) Twenty normal full-term infants were given irradiated evaporated milk as their sole source of oral vitamin D during three to six months between October and April. At the end of three months one infant showed radiological evidence of mild active rickets and two of healed rickets.

(2) Seven infants suffering from active rickets were treated as in-patients with irradiated evaporated milk as their sole source of vitamin D. Evidence of healing was seen in all cases in from one to three weeks.

(3) It is concluded that although the brand of irradiated evaporated milk used will serve to protect the majority of full-term infants from manifest rickets, it cannot be relied on to do so in all cases.

(4) That the milk in question has considerable anti-rachitic properties is shown by the response of the rachitic group of infants. It should therefore serve as a valuable source of vitamin D, particularly in the case of infants who receive vitamin D supplement irregularly or in insufficient amount. The milk should not, however, be relied on as the sole source of vitamin D, particularly in the case of prematures.

(5) The milk was found easy to use, and was taken well by the great majority of infants. No ill effects were observed from its prolonged administration.

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THE CAUSE OF REDUCTION OF THE SUGAR CONTENT OF THE CEREBROSPINAL FLUID IN MENINGITIS

BY

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Reduction in the glucose content of the cerebrospinal fluid is a familiar finding in all forms of meningitis, but the cause of this has not yet been definitely determined. In a previous communication (1939) it was shown that it is not due to diminution in blood sugar content, and it appears that the phenomenon must be due either to too little sugar entering the cerebrospinal system on account of pathological changes in the blood-brain barrier or to glycolysis within the fluid itself.

The work of Dandy (1919) and Weed (1914) established beyond doubt that the source of origin of the cerebrospinal fluid is the choroid plexus in each of the lateral ventricles, and, in view of the widespread changes which are known to occur in this area in meningitis, it seems reasonable to suppose that the permeability of the plexus will be affected. Tcherkassov and Jolkver (1935) believe that the plexus undergoes changes in all forms of meningitis and, as recovery takes place, normal function is restored. Weichsel and Herzger (1936) explain the diminution in cerebrospinal fluid sugar on the basis of diminished circulation of blood through the plexus with a raised threshold for sugar. In support of their views they quote the work of Walter (1929), who finds an increased passage of protein and bromides in inflammatory conditions of the meninges though the sugar threshold is above normal. Linder and Carmichael (1928), on the other hand, exclude the possibility of changes in permeability on the grounds that the reduction in the chlorides of the cerebrospinal fluid in meningitis is proportionate to the reduction in serum chlorides.

The alternative that sugar is secreted in normal amount and subsequently destroyed in the cerebrospinal fluid remains to be considered.

Kopetzky (1933) found experimentally that raised intracranial pressure, by interfering with the cerebral circulation, caused lessened oxidation in the affected area, and in conjunction with Fishberg (1933) suggested that anaerobic glycolysis takes place with excessive formation of lactic acid. It is well known that the lactic acid content of the cerebrospinal fluid in meningitis is above normal and that, owing to over-production of cerebrospinal fluid, the intracranial pressure is

raised, but it seems unlikely that these two factors bear any relationship to one another.

Chevassut (1927) claims that there is a glycolytic ferment in normal cerebrospinal fluid, but she does not show that this is increased in meningitis, though she suggests that in pathological conditions the action of the ferment is accelerated by the presence of cells or organisms. Tcherkassov and Jolkver (1935) believe that such a ferment may be the cause of reduction in cerebrospinal fluid sugar content in meningitis, but show no experimental proof of this. Other workers, Fasold and Schmidt (1929) and Rimele (1938), are unable to detect glycolysis in normal sterile cerebrospinal fluid even after allowing it to stand for several days.

It has been suggested that the presence of bacteria or an excess of leucocytes in the cerebrospinal fluid may be the cause of this lowering of sugar in meningitis. Soedjono (1938) found that the addition of *b. coli*, *staphylococci* or *pneumococci* to normal cerebrospinal fluid brought about almost complete glycolysis in two to three days, while Rimele (1938) found this to be the case only on addition of *b. coli* or *b. subtilis*.

It is known that normal blood removed from the body and kept under sterile conditions decreases in sugar content. McLeod (1921) is of the opinion that glycolysis is brought about by the action of both red and white cells, and that suspensions of leucocytes, such as dilute pus, are strongly glycolytic. Barron and Harrop (1929) hold that the white cells of the blood have a much higher metabolic activity than the erythrocytes and that polymorphonuclears have five times the glycolytic power of lymphocytes.

Levene and Meyer (1912) were the first to test the sugar-destroying power of leucocytes *in vitro*. They obtained sterile polymorphic exudates by injection of 1.5 c.c. of turpentine into the pleural cavity of dogs, centrifuged the aspirated fluid, and added the resulting deposit of cells to sterile Henderson phosphate mixture to which glucose had been added. After incubation reduction in the sugar content of the supernatant fluid was found.

Investigating the action of white cells on spinal fluid, Soedjono (1938) found that in normal cerebrospinal fluid with cell counts ranging from 3 to 15 per c.mm., kept under sterile conditions from six to ninety-six hours at room temperature or 0° C., there was no change in sugar content and no glycolysis when extra sugar was added. Cerebrospinal fluid from cases of meningitis left standing showed reduction of sugar content in six hours, in which time added glucose had also disappeared. These changes were most marked in fluids from purulent meningitis, less so in those from tuberculous cases. After adding white blood cells to normal cerebrospinal fluid, he demonstrated glycolysis which was proportional to the number of cells added. No breakdown of sugar resulted when lymphocytes were used instead of polymorphonuclear cells, a finding which supports the work of Barron and Harrop (1929).

From the foregoing review of the literature it seems unlikely that lessened permeability of the choroid plexus to the passage of sugar into the cerebrospinal fluid is the cause for the reduction in its sugar content in meningitis. The evidence points to the reduction being due to the action either of bacteria or of white blood corpuscles.

Present investigation

Tests were devised to determine in meningitis : (1) if there is alteration in the permeability of the blood-brain barrier to glucose ; (2) if the action of

bacteria is the cause of the reduction of sugar in the cerebrospinal fluid ; or (3) if the presence of leucocytes is responsible for the reduction.

Methods.—The spinal fluid sugar was estimated by a modified Folin-Wu (1920) method using 1 c.c. of fluid. The lactic acid content of 0·5 c.c. of blood or spinal fluid was estimated colorimetrically with hydroquinone after precipitation of protein by sodium metaphosphate and sulphuric acid, and of carbohydrate by calcium hydroxide and copper sulphate.

1. Alteration in the permeability of the blood-brain barrier.—The opportunity was afforded to examine the sugar content of the cerebrospinal fluid before and after the intravenous injection of glucose in one case of cerebral diplegia and in one of miliary tuberculosis, in both of which the cerebrospinal fluid was normal. These cases served as controls. Similar tests were carried out in seven cases of tuberculous meningitis. The results are shown in table I. From this it will be seen that in five of the seven cases of meningitis there was a relatively greater rise in the sugar content of the spinal fluid after the administration of glucose intravenously than in the two control cases. In the case of M.A.M. it is possible that insufficient allowance was made for the time lag which occurs in the reaction of the cerebrospinal fluid to the intravenous injection of glucose, as the second specimen of cerebrospinal fluid was examined only half an hour after the injection was given. In the case of R. McN. the rise is almost as great as that found in one of the control cases.

TABLE I
TO SHOW THE INCREASE IN CEREBROSPINAL FLUID SUGAR CONTENT AFTER
 $\frac{1}{2}$ GM. GLUCOSE PER KGM. BODY WEIGHT GIVEN INTRAVENOUSLY

NAME	C.S.F. SUGAR, MGM. PER CENT.			PERCENTAGE INCREASE IN C.S.F. SUGAR CONTENT	DIAGNOSIS
	BEFORE INJECTION	TIME, HOURS	AFTER INJECTION		
J. H. . .	60	1	98	63	Miliary tuberculosis
G. McA. . .	61	1½	86	40	Spastic diplegia
M. McM. . .	33	½	55	66	Tuberculous meningitis.
M. A. M. . .	32	½	35	9	" "
J. G. . .	11	½	32	190	" "
C. B. . .	20	½	57	172	" "
M. McG. . .	13	1	30	130	" "
J. B. . .	14	1	27	92	" "
R. McN. . .	31	1	42	35	" "

It would appear from these tests that there is no interference with the permeability of the blood-brain barrier to glucose. Further support to this view is afforded by the finding of normal values for non-protein nitrogen content of blood and cerebrospinal fluid in all forms of meningitis at all stages of the disease and by the fact that normal figures were obtained for the ratio of blood chloride to cerebrospinal fluid chloride in both purulent and tuberculous meningitis. The results for chloride estimations have already been reported (Hendry, 1939) and are in agreement with those of Linder and Carmichael (1928).

Further evidence against diminished permeability of the choroid plexuses and in favour of glycolysis being the cause of reduction in the cerebrospinal fluid sugar content is afforded by a study of the lactic acid content of the blood and the cerebrospinal fluid. It is known that lactic acid is one stage in the breakdown of glucose to CO_2 and H_2O , and if the lactic acid content of the spinal fluid can be shown to be increased above normal it is evidence that the glycolysis is taking place in the fluid. According to previous workers (tables 2 and 3), the normal ratio of cerebrospinal fluid lactic acid to blood lactic acid is 0·6 to 1·0 and the normal cerebrospinal fluid lactic acid content 6 to 30 mgm. per cent. In meningitis, on the other hand, it is generally agreed that there is no alteration in the blood lactic acid content, but that there is a considerable increase in the amount of the acid in the cerebrospinal fluid, indicating that glycolysis takes place there. Geldrich (1934) quotes 120 to 150 mgm. per cent. for his series of meningitis cases, and believes that any value over 40 mgm. per cent. should be regarded as pathological, whereas Kopetzy and Fishberg (1933) found the ratio of cerebrospinal fluid lactic acid to blood lactic acid ranged from 3·0 to 4·0.

TABLE 2
NORMAL CONTENT OF LACTIC ACID IN CEREBROSPINAL FLUID

OBSERVER	C.S.F. LACTIC ACID IN MGM. PER CENT.	
	MAXIMUM	MINIMUM
Geldrich (1934)	20	10
Wright, Herr and Paul (1931)	30	6
De Sanctis, Killian and Garcia (1933)	15	8
Glaser (1926)	27	11
Hendry (present series)	30	7

TABLE 3
NORMAL RATIO OF CEREBROSPINAL FLUID TO BLOOD LACTIC ACID

OBSERVER	MAXIMUM RATIO	MINIMUM RATIO
De Sanctis, Killian and Garcia (1933)	0·80	0·90
Wright, Herr and Paul (1931)	0·80	—
Kopetzy and Fishberg (1933)	1·00	0·60
Hendry (present series)	1·00	0·52

In the present series whilst blood lactic acid readings were within normal limits, the cerebrospinal fluid lactic acid ranged from 25 to 200 mgm. per cent. and the ratio from 0·8 to 2·3. In meningococcal cases, as recovery took place and the sugar content of the cerebrospinal fluid rose, the lactic acid content fell, whilst in tuberculous meningitis as the condition worsened and the sugar content of the cerebrospinal fluid fell the lactic acid content rose. Fig. 1 and 2 demonstrate these findings in typical cases.

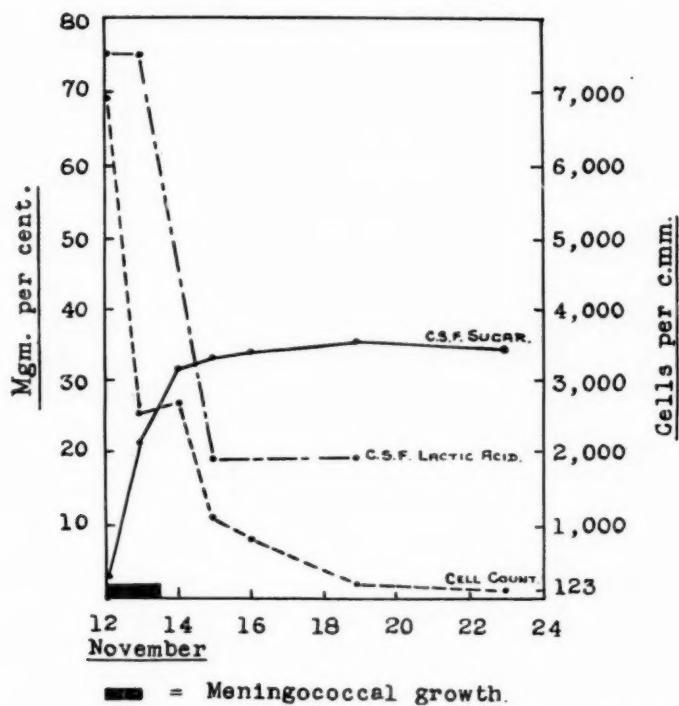


FIG. 1.—Changes in the sugar and lactic acid content and cell count of the cerebrospinal fluid in the course of meningococcal meningitis.

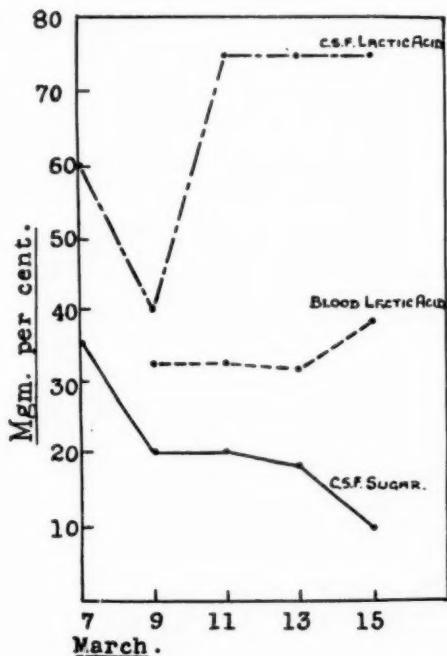


FIG. 2.—Changes in the sugar and lactic acid content of the cerebrospinal fluid and in the blood lactic acid content in tuberculous meningitis.

2. Tests to determine if the presence of bacteria is the cause of the decrease in cerebrospinal fluid sugar content in meningitis.—Five c.c. of sterile cerebrospinal fluid were incubated with 0·01 c.c. of bacterial emulsion (2,000,000,000 organisms per c.c.). Fluid removed for the purpose of encephalography enabled sufficient to be available from a single patient to provide a control tube of fluid and five others to each of which was added one of five different strains of bacteria. The organisms selected for the test were meningococcus, pneumococcus, *b. coli*, staphylococcus albus and staphylococcus aureus. In table 4 the results are shown of sugar estimations in the control before incubation and in all six specimens twenty-four hours after incubation. From this it will be seen that *b. coli* proved to be actively glycolytic, whilst no glycolysis was brought about by the other four types of bacteria, any difference in the glucose content of the respective four fluids before and after incubation being well within the bounds of experimental error.

TABLE 4

TO SHOW THE EFFECT ON SUGAR CONTENT OF INCUBATING 5 C.C. OF NORMAL CEREBROSPINAL FLUID INOCULATED WITH 0·01 C.C. BACTERIAL EMULSION (2,000,000,000 BACTERIA PER C.C.) FOR TWENTY-FOUR HOURS

CONTROL C.S.F., MGM. PER CENT.		INOCULATED C.S.F. AFTER 24 HOURS INCUBATION, MGM. PER CENT.				
BEFORE INCUBATION	AFTER INCUBATION	C.S.F. AND STAPH. ALBUS	C.S.F. AND STAPH. AUREUS	C.S.F. AND MENINGO- COCCI	C.S.F. AND PNEUMO- COCCI	C.S.F. AND <i>B. COLI</i>
59·25	58·39	55·55	55·94	57·55	60·0	Sugar absent

A similar test was carried out later with a human strain of *b. tuberculosis*. No glycolysis occurred after twenty-four hours' incubation, a finding in agreement with the work of Loebel, Shorr and Richardson (1933), who reported almost negligible breakdown of glucose to lactic acid by this organism.

3. Tests to determine if the presence of leucocytes causes reduction in the sugar content of the cerebrospinal fluid.—To a test-tube containing sterile normal cerebrospinal fluid, leucocytes obtained from the centrifuged sediment of citrated normal blood were added. A cell count was made and the fluid incubated at body temperature for twenty-four hours. A control specimen of the same cerebrospinal fluid to which leucocytes had not been added was incubated under the same conditions. Sugar estimations were made on the control specimen before incubation and on both specimens after incubation, when cultures were taken in order to exclude the possibility of glycolysis being due to bacterial contamination. In six experiments in which the resulting culture was sterile, a reduction was found in the amount of glucose in the cerebrospinal fluid to which white blood cells had been added, but none in the control specimen. The results are set out in table 5, and it will be noted that the decrease in sugar content is roughly in proportion to the number of added cells, a finding

which corresponds to those of Soedjono (1938). Table 6 shows a similar test in which lymphocytes were added to a cerebrospinal fluid one other specimen of which was treated as above with white blood cells and a third specimen used as a control. The lymphocytes were obtained from the centrifuged sediment of a specimen of pleural exudate the film of which showed 100 per cent. lymphocytes and the culture of which was sterile. As it so happened, the resulting cell counts were close for both lymphocytes and white blood cells. The reduction in sugar content in the fluid to which lymphocytes were added is almost negligible and within the 5 mgm. per cent. limit of experimental error, whilst the reduction in sugar when white blood cells were used is in keeping with the results of the other five tests.

TABLE 5

TO SHOW THE EFFECT ON SUGAR CONTENT OF ADDING WHITE BLOOD CELLS TO NORMAL CEREBROSPINAL FLUID—SUGAR ESTIMATIONS BEFORE AND AFTER INCUBATION

CASE	CONTROL C.S.F., MGM. PER CENT.		C.S.F. AND W.B.C. AFTER INCUBATION, MGM. PER CENT.	CELL COUNT, PER C.MM.	CULTURES
	BEFORE INCUBATION	AFTER INCUBATION			
1	72.07	72.07	32.0	3,200	Sterile
2	70.17	66.09	40.0	2,400	"
3	50.36	50.36	15.27	8,000	"
4	100.0	101.6	44.44	16,000	"
5	51.61	52.20	36.54	1,800	"
6	87.9	91.0	6.29	10,800	"

TABLE 6

TO SHOW THE EFFECT ON SUGAR CONTENT OF ADDING WHITE BLOOD CELLS AND LYMPHOCYTES TO NORMAL CEREBROSPINAL FLUID—SUGAR ESTIMATIONS BEFORE AND AFTER INCUBATION

CONTROL C.S.F. MGM. PER CENT.		C.S.F. AND W.B.C., 2,400 PER C.MM. MGM. PER CENT.	C.S.F. AND LYMPHOCYTES, 2,800 PER C.MM. MGM. PER CENT.
BEFORE INCUBATION	AFTER INCUBATION		
64.0	64.0	29.9	59.3

Cultures all sterile.

From these findings it may be concluded that white cells have a glycolytic action on the sugar of normal spinal fluid and that this is probably due to polymorphonuclear cells rather than to lymphocytes.

Discussion

The above findings suggest an explanation for the changes in the cerebrospinal fluid sugar content found in meningitis. In the early stages of cerebro-

spinal fever a greatly increased cell count and a positive bacterial culture are almost invariably found. At this time the sugar content is extremely low. The present series of cases was treated with sulphanilamide, and it was customary to find a sterile cerebrospinal fluid on the second or at the latest on the third occasion on which lumbar puncture was performed. As at this stage of the illness the cell count is still high and the sugar content, though rising, well

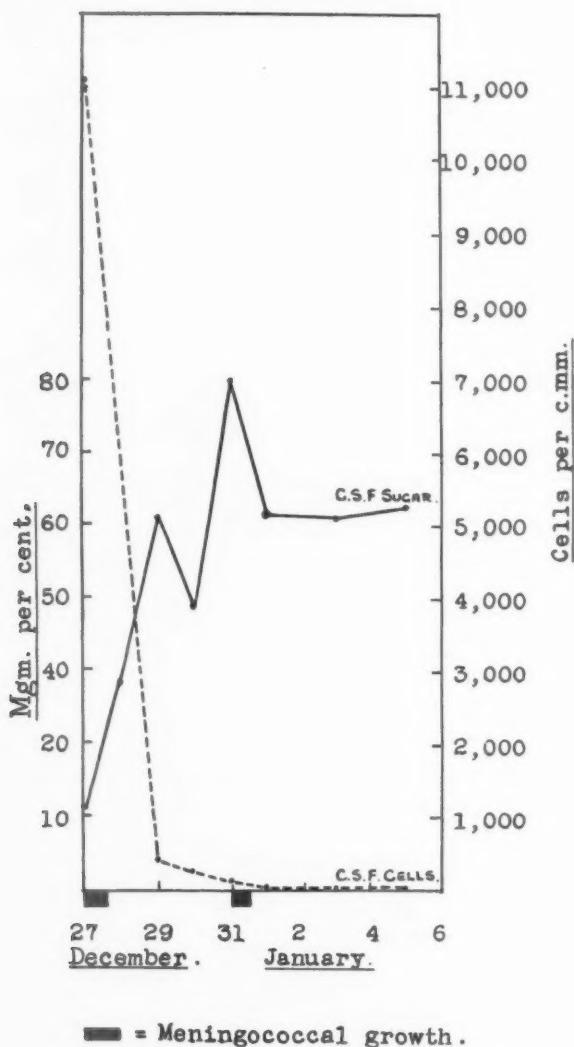


FIG. 3.—To show that the presence of meningococci in the cerebrospinal fluid does not influence its sugar content.

below normal limits, these findings would suggest that meningococci are not responsible for the breakdown of glucose. Fig. 3 shows the sugar and cell count changes in a typical case. It is interesting to note that, on the fourth day after the fluid had become sterile, there was a recurrence of a positive bacterial culture and that this had no effect on the sugar content, which, like the cell count, was returning to normal limits.

An observation noted in these cases of meningococcal meningitis throws some light on the question whether polymorphonuclear cells or lymphocytes are responsible for the reduction in the cerebrospinal fluid sugar content. In the course of recovery the cell picture of the fluid changes from being almost entirely polymorphonuclear to being largely composed of lymphocytes. In the early stages there is great reduction in the cerebrospinal fluid sugar content, whilst in the later stages when the exudate is largely composed of lymphocytes the sugar content approaches the normal level. Further, in conditions such as benign lymphocytic meningitis, in which there is a purely lymphocytic exudate, there is no sugar reduction in the spinal fluid.

Two cases of meningitis due to *b. coli* showed complete absence of cerebrospinal fluid sugar, an occurrence which might be expected in view of the fact

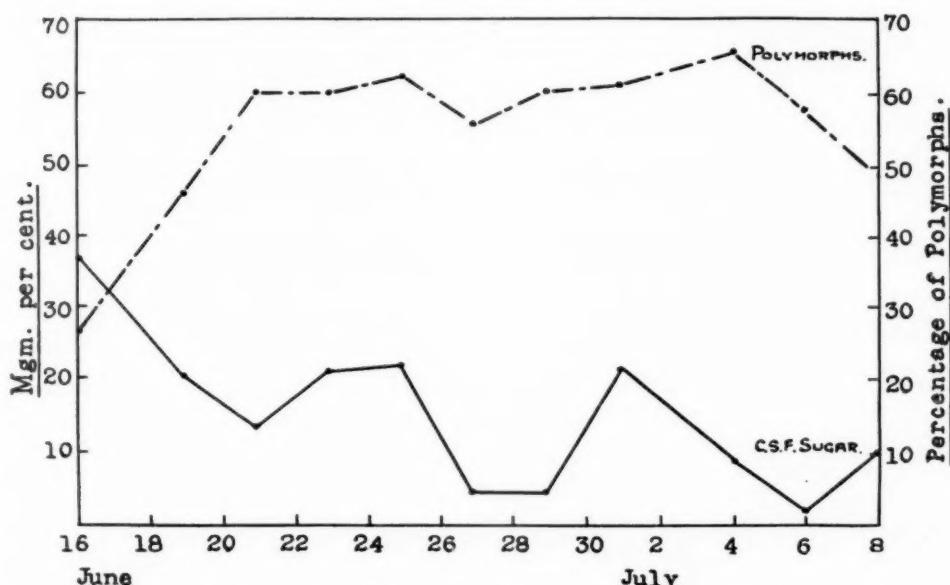


FIG. 4.—To show the effect on the sugar content of increase in the number of polymorphonuclear leucocytes in the cerebrospinal fluid in tuberculous meningitis.

that two factors are at work, a strongly glycolytic organism in addition to a large polymorphic cellular exudate.

From the findings in tuberculous meningitis, conclusions are not so easily drawn, but some suggestions may be put forward. As the tubercle bacillus has practically no power to break down sugar and as it is present in the cerebrospinal fluid only in small numbers, the part it plays in reduction of cerebrospinal fluid sugar may be neglected.

In the early stages of the disease the cellular exudate in the spinal fluid is largely lymphocytic and at this time the sugar content of the fluid is not greatly below normal. As the disease progresses to its fatal issue, there is an increase in the number of polymorphonuclear cells and a simultaneous decrease in the sugar content. Fig. 4 shows the proportion of polymorphonuclear cells to lymphocytes and the spinal fluid sugar content in a case of

tuberculous meningitis observed from its early stages till death. It demonstrates the fall in the glucose content as the number of polymorphonuclear cells increases.

Conclusions

1. The permeability of the choroid plexus to glucose is not affected in cases of meningitis.
2. Reduction in cerebrospinal fluid sugar in meningitis is due to glycolysis within the cerebrospinal system.
3. The presence of the meningococcus or tubercle bacillus in the spinal fluid is not responsible for the reduction in its sugar content in meningitis due to these organisms. *B. coli* has a glycolytic action and in coliform meningitis the reduction in cerebrospinal fluid sugar is in great part due to this.
4. Polymorphonuclear leucocytes possess powers of glycolysis and their presence is the reason for reduction in cerebrospinal fluid sugar in purulent meningitis and for the progressive decrease in its sugar content in tuberculous meningitis.

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IRON-RESISTANT ANAEMIA AND LATENT RICKETS IN SCHOOLCHILDREN

BY

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The clinical association of rickets and anaemia has often been described and frequently denied.

Of thirty children, aged between one and four years, with active rickets examined by Findlay (1909), only nine were anaemic, and he concluded that the anaemia was due to secondary complications of the rickets. Hess (1929) states that anaemia is usually found in advanced rickets, but is not characteristic. Parsons (1934) says that anaemia is in no sense a symptom of rickets, although a degree of nutritional anaemia is not unusual, because a diet which is defective in one factor is likely to be defective in others. McDonough and Borgen (1937) studied thirty children, aged between six months and three years, with active rickets. Of the nineteen uncomplicated cases, six had haemoglobin values below 60 per cent., whilst only three had values above 80 per cent. Of the eleven complicated cases, six had haemoglobin values below 60 per cent. (two being below 40 per cent.), whilst none had values above 80 per cent. The 'complications' were poor diet, cleft palate, upper respiratory infections, otitis media and suppurative adenitis. Since these authors regard only values below 60 per cent. haemoglobin as indicating anaemia, they conclude that the anaemia seen in rickets is due rather to secondary infection or lack of other nutritional factors than to lack of vitamin D. If 80 per cent. be taken as the minimal normal haemoglobin value for the young child, their figures show only three rachitic children with normal values.

It appears that rachitic children are often, but not always, anaemic. It has not been possible to find any description of anaemia in late rickets or in latent rickets. The work to be described here shows that existence of iron-resistant anaemia in school-children, associated with latent or chemical rickets, and the therapeutic results seem to indicate a close connexion between the anaemia and the rickets.

Source of cases

The cases were sent by the medical officer of the Hoxton and Star Cross L.C.C. Nutrition Clinics. Cases reach these clinics from five sources : (1) school medical officers ; (2) care committees, who deal with poor families ;

(3) minor ailments clinics ; (4) sun-ray clinics ; (5) direct requests by parents. Of a hundred and thirty-one children seen at these two nutrition clinics between 1936 and the middle of 1938, fifty-two had haemoglobin between 80 and 85 per cent., whilst a further twenty-three had haemoglobin below 80 per cent. All children in whom the anaemia failed to respond to iron in doses of ferrous sulphate 3 grains t.d.s. or Blaud's capsules 15 grains t.d.s., as well as a few untreated anaemic children, were referred to the Royal Free Hospital. Eighteen children in all were examined. Their ages ranged from five and a half to twelve years. The investigations were done between January and September, 1938, but the majority were in the first quarter of the year.

Method

A full history was taken from each parent, with special reference to whether signs of rickets were or had been present. Each child was subjected to a complete physical examination, and the wrists and fore-arms were x-rayed for evidence of rickets. Blood was removed by venupuncture, part into an oxalate mixture. The oxalated blood was used for the estimation of inorganic phosphorus, haemoglobin, total red cell count and mean corpuscular volume. The serum was used for the estimation of the serum calcium. The haemoglobin was estimated by Haldane's method, the inorganic phosphorus by Briggs' modification (1922) of the Bell-Doisy method and the serum calcium by the Clark-Collip modification (1925) of the Kramer-Tisdall method. Any child with a haemoglobin percentage below 85 per cent. was regarded as definitely anaemic, and any child with a calcium-phosphorus product below 40 as suffering from latent rickets.

To ensure that the anaemia was truly iron-resistant, each child was treated with ferrous sulphate 5 grains b.d. for four weeks. Each was then given four 50,000 international unit tablets of vitamin D concentrate (200,000 units of vitamin D in all), and the dose repeated after one fortnight. After one month on vitamin D only, ferrous sulphate, 5 grains b.d., was added, and thus for the last four weeks of treatment each child received 100,000 units of vitamin D and 70 grains of ferrous sulphate per week. Clinical and blood examinations were done throughout at fortnightly intervals.

So massive a dosage with vitamin D was adopted for two reasons. The first was that this 'vitamin Stoss' therapy has been highly recommended by Harnapp (1936a, b) and Braulke (1937) in cases in which rapid improvement in rickets is required. Braulke gave single doses of 600,000 I.U. of vitamin D with satisfactory results and no ill-effects in fifty children. The second reason was that the swallowing of the tablets could be personally supervised in these out-patient children and thus failures due to their not having been taken at home were avoided. None of the children showed any ill-effects from these massive doses. The maximum dose in any child was 800,000 I.U. over a period of eight weeks.

Results

Initial findings.—Table 1 gives a summary of the initial findings in the eighteen children. The lowest haemoglobin reading was 71 per cent. and the highest 85 per cent. The colour indices varied between 0·84 and 0·97. The mean corpuscular volumes varied between 78 and 98 cubic μ . The serum calcium values varied between 9·11 and 11·00 mgm. per 100 c.c. (normal range 9 to 11 mgm. per 100 c.c.). With the exception of cases 6, 8, 9 and 10, the inorganic phosphorus values varied between 2·16 and 3·88 mgm. per 100 c.c., the mean being 3·15 mgm. per 100 c.c. (normal range in children between five and twelve years : 4·0—5·5 mgm. per 100 c.c.). Cases 6, 8, 9 and 10 had phosphorus values within normal limits. The cases with low phosphorus values had correspondingly low calcium-phosphorus products ($Ca \times P$).

TABLE I
INITIAL FINDINGS

CASE NO.	SEX	AGE IN YEARS	DURATION OF PREVIOUS IRON TREATMENT	HÆMOGLOBIN PER CENT. (HALDANE)	RED BLOOD CELLS (MILLIONS PER C.M.M.)	COLOUR INDEX	MEAN CORPUSCULAR VOLUME IN CU. μ .	Ca (MGM. PER 100 CC. SERUM)	P (MGM. PER 100 C.C. BLOOD)	Ca \times P
1	F	9	2 months	77	4·05	0·96	95	9·41	3·34	31·5
2	F	8½	4 months	77	4·19	0·92	—	9·11	3·81	34·4
3	F	9	1 year	83	4·44	0·94	79	10·37	3·15	32·7
4	F	10	—	85	4·59	0·93	78	9·38	3·10	30·1
5	F	8	—	74	3·96	0·93	98	10·37	2·78	29·0
6	F	5	2 years	76	4·07	0·93	84	9·26	4·46	41·3
7	F	12½	15 months	80	4·35	0·90	89	9·80	3·33	32·6
8	M	5½	—	80	4·77	0·84	—	10·32	4·26	45·5
9	M	7	—	74	3·86	0·96	—	10·56	4·37	46·1
10	M	11	—	80	4·32	0·90	—	9·26	4·63	43·0
11	M	12	5 months	86	4·47	0·93	88	9·72	2·16	21·0
12	F	6	6 months	75	4·00	0·90	92	10·15	2·76	28·0
13	M	9	6 months	76	4·10	0·90	93	10·50	2·90	30·5
14	F	6	1½ years	83	4·75	0·89	85	9·22	3·60	33·2
15	M	6	3 months	71	4·42	0·81	86	10·48	2·08	21·8
16	M	6	2 months	83	3·65	0·93	94	10·40	3·73	38·8
17	F	8½	1 year	76	3·90	0·97	97	10·37	3·88	40·3
18	M	8	4 months	85	4·43	0·96	—	11·00	3·50	38·0

Cases 1, 4, 8, 15 and 17 showed clinical evidence suggestive of old rickets (slight bossing of the skull, slight enlargement of the epiphyses, or rickety rosaries). In none of them was there anything suggestive of florid rickets. On x-ray cases 16 and 17 showed irregularity of the radial and ulnar epiphyseal lines, suggestive of rickets. Cases 1 and 18 showed clinical chorea without cardiac involvement. Cases 3 and 4 and cases 7 and 18 were sisters, cases 9 and 10 were brothers, and cases 12 and 13 were siblings. Case 5 was a high-grade mental defective. Cases 4, 5, 8, 9 and 10 had received no previous iron therapy.

Of the four children with normal phosphorus values, three were not seen

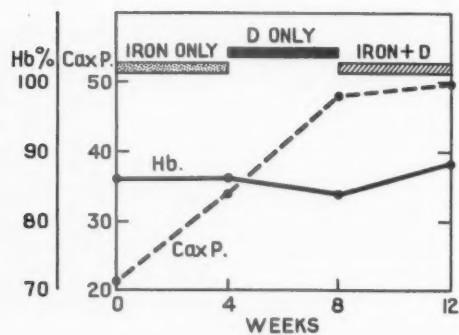


FIG. 1.—Case 11.

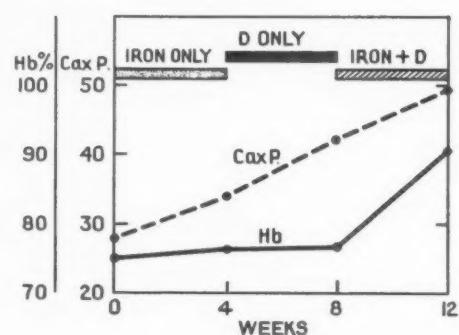


FIG. 2.—Case 12.

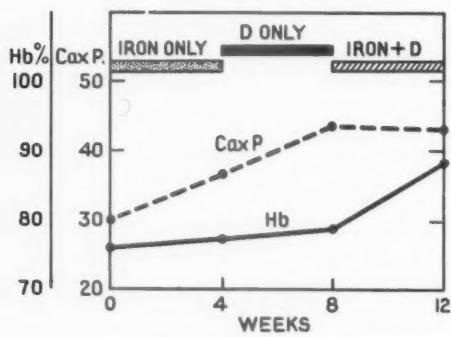


FIG. 3.—Case 13.

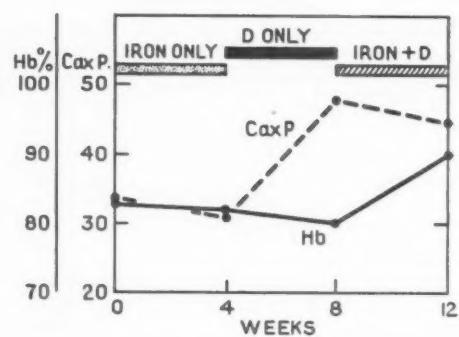


FIG. 4.—Case 14.

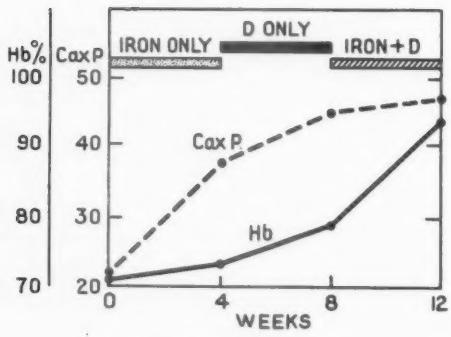


FIG. 5.—Case 15.

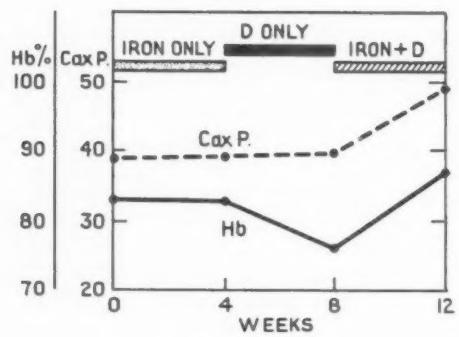


FIG. 6.—Case 16.

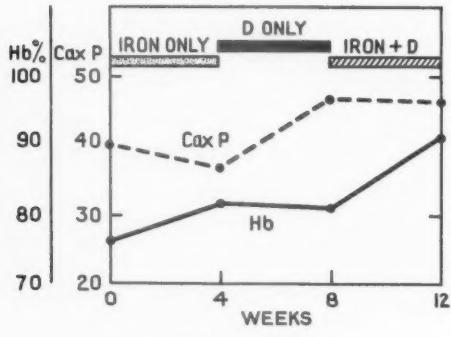


FIG. 7.—Case 17.

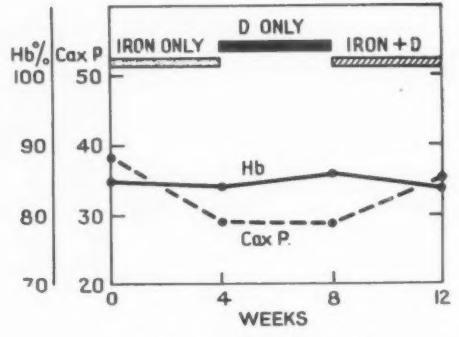


FIG. 8.—Case 18 (Chorea).

again. The fourth, case 8, responded rapidly to iron. Only one of the four, case 6, had received previous iron therapy. Excluding these four and the two children with chorea, cases 1 and 18, the remaining twelve children present a definite clinical picture of orthochromic, normocytic or hypochromic microcytic anaemia associated with a low inorganic blood phosphorus, without gross physical signs of rickets. In all but two, this anaemia had been adequately treated with iron, and had failed to respond.

Results of treatment.—Owing to non-attendance, only eight children (cases 11–18) could be subjected to the full scheme of treatment. The results of this treatment are shown in table 2 and fig. 1–8. Two children showed slight increases in haemoglobin on either iron or vitamin D alone (cases 15 and 17). The remainder showed no significant increase. In every child except case 18, vitamin D restored the blood phosphorus to normal. Further, in every child except case 18, a combination of iron and vitamin D restored the haemoglobin to normal. Excluding case 18, the mean haemoglobin reading after iron alone and vitamin D alone was 79 per cent. After a combination of iron and vitamin D, the mean was 89 per cent. Case 18 was suffering from chorea, and, in spite of a rise in blood phosphorus, her haemoglobin was unaffected by treatment.

TABLE 2
RESULTS OF TREATMENT

CASE NO.	INITIAL FIGURES			AFTER IRON ALONE			AFTER VITAMIN D ALONE			AFTER IRON + VITAMIN D		
	HAEMOGLOBIN	P MGM. PER CENT.	Ca X P	HAEMOGLOBIN	P MGM. PER CENT.	Ca X P	HAEMOGLOBIN	P MGM. PER CENT.	Ca X P	HAEMOGLOBIN	P MGM. PER CENT.	Ca X P
11	86	2.16	21.0	86	4.01	34.0	84	4.71	48.0	88	4.76	49.8
12	75	2.76	28.0	76	3.01	33.4	76	4.26	41.8	90	4.86	48.6
13	76	2.90	30.5	77	3.29	36.5	79	4.59	43.9	88	4.34	43.0
14	83	3.60	33.2	82	2.95	31.5	80	4.76	47.6	90	4.47	44.7
15	71	2.08	21.8	74	3.51	37.7	79	4.50	44.7	94	4.47	46.9
16	83	3.73	38.8	83	3.73	38.8	76	4.27	39.5	87	4.40	48.5
17	76	3.88	40.3	82	3.87	36.3	81	4.42	46.7	91	3.91	46.0
18	85	3.50	38.0	84	2.62	29.1	86	2.98	29.1	84	4.05	35.1

Conclusions

From the results it is justifiable to state that a mild iron-resistant hypo- or orthochromic anaemia associated with latent low-phosphorus rickets, is to be found among school-children. The low blood phosphorus is rapidly corrected by massive doses of vitamin D, but the anaemia is relieved only by a combination of iron and vitamin D. It appears that adequate supplies of vitamin D are essential in these children if iron is to be properly utilized for blood formation.

Summary

1. In twelve children, aged between six and twelve and a half years, an iron-resistant hypo- or orthochromic anaemia was found, associated with a low inorganic blood phosphorus, but with no definite clinical signs of rickets.
2. Vitamin D, given in two single doses of 200,000 international units at fortnightly intervals, restored the blood phosphorus values to normal in one month, but had no effect on the haemoglobin values.
3. A combination of similar doses of vitamin D and ferrous sulphate, 5 grains b.d., raised the mean haemoglobin readings from 79 per cent. to 89 per cent. in one month.

Thanks are due to Miss Lucy Wills for her constant help and encouragement. The calcium and phosphorus estimations were done under her supervision. Thanks are also due to the medical staff of the L.C.C. for arranging that the children should be sent to us ; to Dr. H. Chodak Gregory for allowing the children to be seen at the Royal Free Hospital ; and to Dr. Ulysses Williams for taking the x-ray pictures and reporting on them. The 50,000-unit vitamin D tablets were kindly supplied by Messrs. Glaxo Ltd.

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PNEUMONIA IN THE NEW-BORN

BY

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PART I

It is only within comparatively recent years that the prevalence of pneumonia among new-born infants has begun to be recognized. Since the work of Hess-Thaysen (1914) first called attention to the great frequency of this disease, several workers (Browne, 1921, 1922; Johnson and Meyer, 1925; Cruickshank, 1930; Chase, 1935) have published the results of investigations of large series of cases, all proving that pneumonia is one of the principal causes of neonatal death. In spite of this it is probable that its great frequency has not yet been fully realized. This is largely due to the difficulty of clinical diagnosis, which is such that the vast majority of cases are not recognized unless a necropsy is performed, and even then, in many cases, only if the pathologist has experience of neonatal pathology and takes special care. As a result, the prevention of this disease receives in many quarters less attention than it deserves. This may be explained in part by a lack of clear knowledge of the causes and pathogenesis of neonatal pneumonia, for in spite of a considerable amount of pathological study much doubt and disagreement still exist as to the mode of infection, the relative importance of infection received before and after birth, the principal causative bacteria and on other fundamental questions. In particular, an extensive study of the literature showed that little attention has been paid to pneumonia developing after the first few days of life, and that knowledge of the bacteriology of all types of pneumonia in the neonatal period is surprisingly scanty.

Present investigation

The investigation of which an outline is now presented was undertaken in the hope that further study of the pathological features and bacteriology of pneumonia and allied pulmonary infections occurring before birth and during the first four weeks of postnatal life, and fuller understanding of the special features of the neonatal period that influence the onset and course of respiratory disease, might shed fresh light on this subject and indicate some of the lines along which the problem of prevention might profitably be approached.

The investigation consisted of a pathological examination of 541 consecutive necropsy cases of infants up to twenty-eight days old, among which 177 cases presented inflammatory changes in the lungs. Every case was subjected to

microscopic examination, as it is recognized that the macroscopic diagnosis of neonatal pneumonia is often difficult and uncertain, especially when the lungs are unexpanded and unaerated and the pneumonia is accompanied by congestion, oedema and haemorrhage, as is often the case. Bacteriological examinations were made in 474 of the 541 necropsies, including 150 cases of pneumonia. The procedure included the examination of films and cultures from the lungs in every case, and of Gram-stained sections of lung in every case of pneumonia. Cultures were made from the heart blood in 250 cases, including 76 cases of pneumonia. The investigation included the examination of the clinical record of every case of pneumonia, as a knowledge of the facts of the maternal and obstetrical history is essential for a proper understanding of the pathological process and its possible causes, especially in the case of the youngest infants.

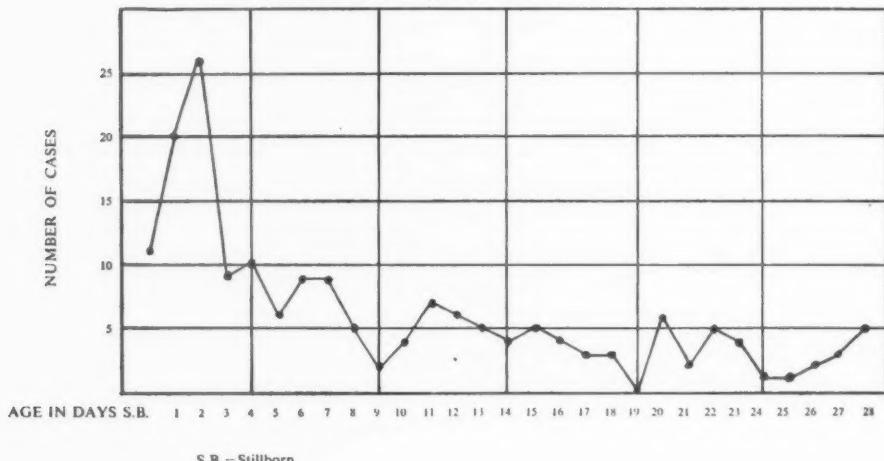
The 541 infants who made up the whole series examined post-mortem included 93 who were born dead and 448 who were born alive and survived not more than twenty-eight days. Among these there were 177 (32.7 per cent.) with inflammatory changes in the lungs, including 11 (11.8 per cent.) among the dead-born and 166 (37 per cent.) among the live-born. This number included three cases in which the inflammatory changes were confined to the bronchi.

Pneumonia was not in all cases the cause of death. A considerable number of the children had other lesions that might have proved fatal of themselves, and in some the pneumonia was of small extent and probably less important than associated conditions. There were, however, many cases in which the pneumonia was the sole and sufficient cause of death, and in all it must be regarded as at least an important contributory factor.

Age incidence.—The chart shows in graphic form the distribution of the pneumonia deaths throughout the twenty-eight days of the neonatal period. Pneumonia occurred in eleven dead-born infants. Eighty-nine (53 per cent.) of the live-born babies died in the first week of life ; 33 (20 per cent.) in the second

CHART

AGE DISTRIBUTION OF 177 CASES OF NEONATAL PNEUMONIA



week ; 23 (13·8 per cent.) in the third week ; 21 (12·6 per cent.) in the fourth week. Forty-six pneumonia deaths (27·7 per cent.) occurred in the first two days, the largest number on any one day being twenty-six on the second. The large excess of deaths in the first week is thus accounted for to a great extent by the heavy mortality in the first two days, some of which is attributable to associated conditions rather than to the pneumonia itself.

Maturity.—According to the commonly accepted standard, infants whose weight at birth exceeded $5\frac{1}{2}$ lb. were regarded as mature, those below that weight as premature. Judged by this standard 100 of the 177 babies with pulmonary inflammation were mature, 77 were premature. It is to be noted that the proportion of premature babies among those who developed pneumonia (43·5 per cent.) is much higher than among all births (estimated at about 10 per cent. for hospital practice). This suggests that premature babies are specially susceptible to respiratory tract infections, an observation previously made by Browne (1922) and others.

Classification.—The pathological study of the 177 cases of pneumonia revealed that they could be divided according to their outstanding pathological characters into four distinct groups, thus :

1. Pneumonia associated with aspiration of contents of the amniotic sac or vagina : (a) in the dead-born (11 cases) ; (b) in the live-born (33 cases).
2. Pneumonia associated with other pulmonary conditions due to stress of birth or otherwise peculiar to the new-born : atelectasis, haemorrhage, (33 cases).
3. Bronchopneumonia and allied types (82 cases).
4. Septicaemia with secondary involvement of the lungs (18 cases).

As a general rule, to which only a few exceptions were found, cases belonging to groups 1 and 2 occurred in infants who were born dead or lived only three or four days after birth ; while those belonging to groups 3 and 4 occurred later, being frequent from the fourth day onward. It was in cases of groups 1 and 2 that the possibility of prenatal infection had to be considered ; those of groups 3 and 4 could, as a rule, be confidently attributed to infection received after birth. These differences in the age incidence of the various groups are shown in the table.

TABLE I
AGE IN RELATION TO PATHOLOGICAL TYPE OF PNEUMONIA

TYPE OF PNEUMONIA	AGE IN DAYS						
	STILL-BORN	0-3	4-7	8-14	15-21	22-28	TOTAL
Prenatal aspiration ...	11	31	2	—	—	—	44
Atelectasis ...	—	11	6	2	1	—	20
Haemorrhage ...	—	7	2	3	1	—	13
Bronchopneumonia and allied types ...	—	6	16	25	18	17	82
Haematogenous lesions	—	—	8	3	3	4	18

The remainder of this paper is occupied with a consideration of the types of neonatal pneumonia that are included in groups 1 and 2. Those belonging to groups 3 and 4 will be discussed in part II.

Pneumonia in the dead-born and in the earliest days of life.—In most cases of pneumonia in the dead-born and in infants who die in the earliest days of postnatal life, the pneumonia is accompanied by some condition of the lungs that must be regarded either as the direct cause or as an important predisposing factor. Chief among such conditions are: (a) aspiration of contents of the amniotic sac or vagina; (b) persistent congenital atelectasis; and (c) massive pulmonary haemorrhage. In the series investigated, all the cases of pneumonia with evidence of prenatal aspiration occurred in infants who died before the end of the fourth day and only three lived more than two days. The other conditions (atelectasis and haemorrhage) were occasionally associated with pneumonia in older infants, but the great majority of those affected died within a week of birth and most of them in the first three days.

Pneumonia associated with prenatal aspiration.—Material aspirated into the lungs of the foetus before or during the process of birth may consist either of contents of the amniotic sac or mucus from the vagina. In this series evidence of aspiration of amniotic sac contents was found much more often (41 cases) than evidence of aspiration of material from the vagina (3 cases).

Pneumonia with evidence of aspiration of contents of the amniotic sac.—This group included all the dead-born infants with pneumonia (11) and 30 live-born, in all of whom there was clear evidence that an excessive quantity of liquor amnii had been drawn into the lungs. The presence of liquor amnii in the lungs is readily detected microscopically by solid material in the fluid (fig. 1). Of the various solid constituents the most often found are cornified

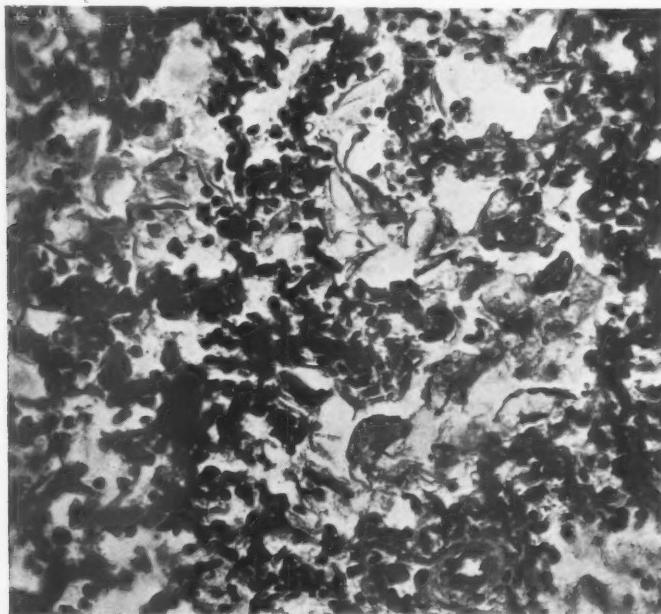


FIG. 1.—Lung of stillborn infant. Cornified cells and other debris from liquor amnii filling alveoli; no pneumonia. H. and E. $\times 250$.

squamous epithelial cells from the skin of the foetus. Lanugo hairs may also be seen. Vernix caseosa is not uncommonly found in the form of amorphous masses lying free in the alveoli or bronchi or adhering to their walls. In live-born infants this material is sometimes found plastered against the walls of alveoli and bronchioles in the form of a continuous membrane. This is referred to again later. Sometimes meconium is found in the lungs. It may be obvious to the naked eye or recognized microscopically by the presence of bile-stained debris (fig. 2).

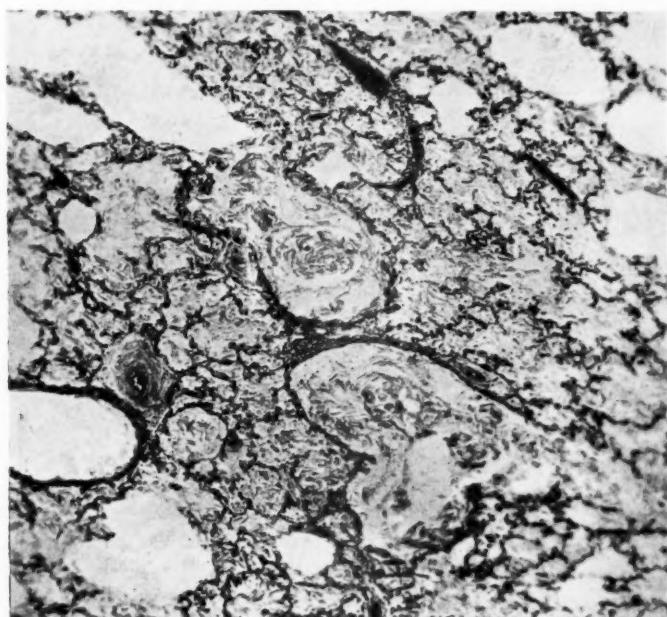


FIG. 2.—Lung of stillborn infant. Bronchioles and alveoli distended with meconium ; no pneumonia. H. and E. $\times 60$.

The significance of finding amniotic sac contents in the lungs of infants has been disputed. Some observers (Ahlfeld, 1888 ; Leff, 1936 ; Snyder and Rosenfeld, 1937) have maintained that the presence of a considerable quantity of liquor amnii in the lungs of the new-born is not abnormal ; while others (Reifferscheid, 1911 ; Farber and Sweet, 1931 ; Helwig, 1933) regarded it as evidence of foetal asphyxia. In the writer's experience when any considerable amount of solid amniotic debris is found in the lungs, there is always other evidence of severe asphyxia, even in the dead-born, in whom the asphyxia could not be attributed to respiratory obstruction due to the presence of abnormal amniotic debris, as suggested by Snyder and Rosenfeld. It appears, then, that while small amounts may be disregarded, any large quantity of amniotic fluid in the lungs is an indication of foetal asphyxia. In all this group of cases, therefore, there was good reason to suppose that the child had been severely asphyxiated during birth.

The pneumonia was often slight in extent but sometimes widespread (fig. 3). Consolidation was not massive and was often difficult to detect at necropsy.

It was accompanied in all cases by atelectasis and by varying degrees of congestion, oedema and haemorrhage. The distribution of the pneumonic exudate was either diffuse or patchy. The bronchi were often little affected ; they might show no inflammation and frequently remained unexpanded. The peribronchitis characteristic of true air-borne bronchopneumonia was not observed.

In eleven cases in live-born infants the condition described by Johnson and Meyer (1925) as 'hyaline membrane' and by Farber and Sweet (1931) and Farber and Wilson (1932) as 'vernix membrane' was observed (fig. 4 & 5).

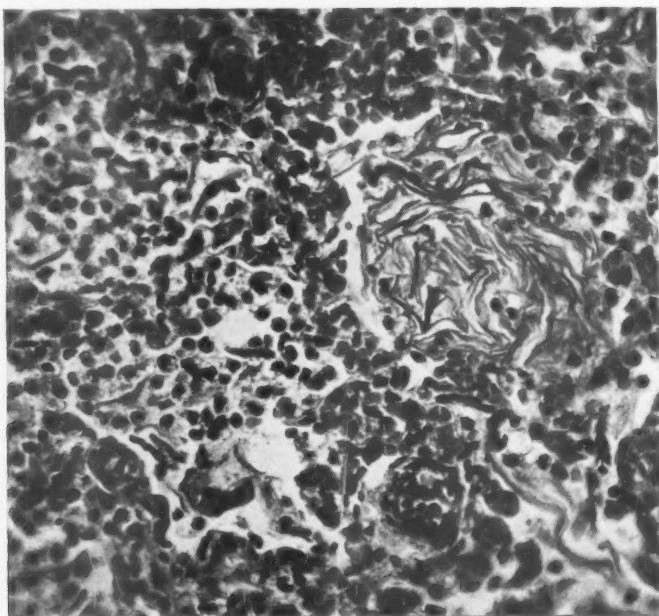


FIG. 3.—Lung of stillborn infant. A patch of pneumonia related to a deposit of amniotic debris. H. and E. $\times 250$.

This consists of homogeneous material, staining strongly with eosin and having a somewhat hyaline appearance, which lines the bronchioles, alveolar ducts, and alveoli with a thick, more or less continuous layer closely applied to the walls. Appropriate staining shows that it usually contains a large amount of fat. It is probable that in most cases, if not in all, it is composed of vernix caseosa, aspirated by the foetus along with liquor amnii. Vernix membrane was found only in live-born infants, though vernix masses were seen in the lungs of several of the dead-born. It is only when air enters the lungs that the material is plastered against the walls of the air-spaces in the form of a membrane. Lungs with vernix membrane always showed more than usually severe atelectasis, and in several cases the small parts that had been aerated showed acute vesicular and interstitial emphysema, with air bullae in the septa and under the pleura, a clear indication of serious obstruction to the passage of air. In keeping with this, these babies always showed at necropsy ample evidence of severe asphyxia, and their clinical records indicated that they had



FIG. 4.—Lung of infant aged two days, showing vernix membrane lining bronchioles, pneumonic exudate and extreme atelectasis. H. and E. $\times 80$.

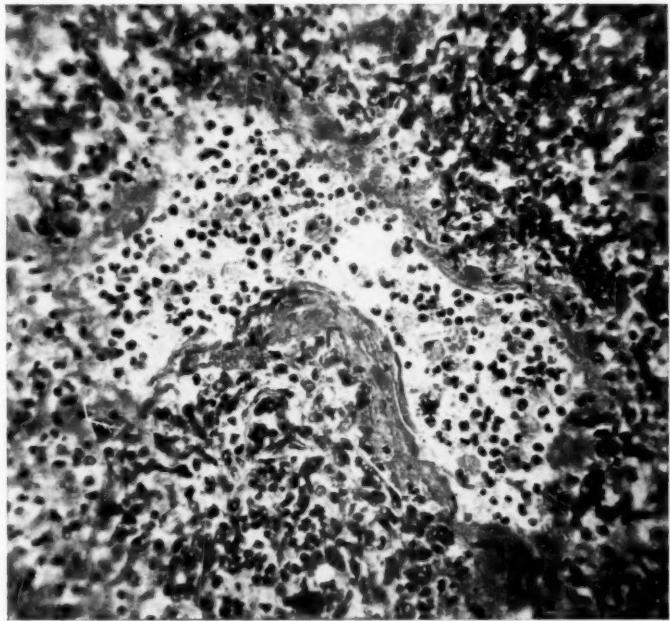


FIG. 5.—Lung of infant three days old. Bronchiole lined with vernix membrane and filled with inflammatory cells. H. and E. $\times 210$.

been badly asphyxiated at birth and failed to breathe well. Vernix membrane often occurs without any inflammatory reaction. When pneumonia is present it has the same characters as in other cases with excessive aspiration of amniotic sac contents.

Many of the infants in whose lungs amniotic sac contents were found had, in addition to pneumonia, other lesions of a lethal character. Sixteen had sustained intracranial injury. Many had suffered severe asphyxia, which might well have proved fatal without pneumonia, and in several the blocking of the air-passages by liquor amnii or meconium was doubtless of greater importance than the pneumonia as a cause of death.

The obstetrical records revealed abnormalities of labour in fifteen cases. These included nine deliveries by forceps, four breech deliveries (two with forceps), two dry labours, two cases of Caesarian section. In one case the liquor amnii was noted to be foetid and the child developed a staphylococcal infection of the lungs with suppuration. In two cases the placenta was noted as being 'unhealthy' but there was no clear evidence of infection of the child from that source. One mother had an antepartum rigor and puerperal septicaemia, but there was no evidence of transplacental infection of her child.

Bacteriological examinations were made in the cases of ten dead-born and twenty-three live-born infants in this group. Among the dead-born six gave negative results, the cultures remaining sterile and examination of films of lung-juice and Gram-stained sections of lungs failing to reveal any bacteria; three gave results that were considered to be inconclusive, as the organisms were probably contaminants; and in one case, in which there was a long dry labour, *b. coli* was considered to be responsible for the pneumonia. Among the live-born three cases gave negative and nine cases inconclusive results, while eleven gave positive results: in one a pure infection with *b. influenzae*, in one a pure infection with *staphylococcus aureus*; in the rest, *viridans* type and indifferent streptococci and coliform bacilli occurred alone or together.

Pneumonia with evidence of aspiration of contents of the vagina.—In three children, who lived twelve, twenty and twenty-nine hours, the bronchi were filled with masses of mucus heavily infected with bacteria, and a severe inflammation had arisen, beginning in the bronchi and spreading to produce extensive consolidation. The lungs contained no recognizable amniotic debris. It seemed probable that the heavily infected material in the bronchi had been aspirated from the genital tract during birth. The bacteria were *streptococcus viridans* in one case, *b. coli* in one and non-haemolytic streptococci together with *b. coli* in the third. One case was a breech delivery, one a forceps delivery with face presentation, one a spontaneous delivery with vertex presentation, but the child was asphyxiated at birth. In all cases, therefore, premature respiratory efforts by the foetus were probable and might have caused aspiration of bacteria-laden mucus from the vagina.

Pneumonia associated with other pulmonary conditions caused by stress of birth or otherwise peculiar to the newborn

Persistent congenital atelectasis.—Lungs in which aspirated amniotic sac contents were found always showed more or less severe congestion and atelectasis and a water-logged condition due to the aspirated fluid. In the cases now to be considered the state of the lungs was similar and the pneumonia assumed the same characters, but no clear evidence of excessive aspiration was found. There were twenty such cases and they all had certain features in common. The lungs were poorly expanded, congested and oedematous. The pneumonia was, in most cases, not very extensive. Its pathological characters were the same as in the cases with aspirated liquor amnii. Almost all the children had exhibited conditions that might explain the persistence of atelectasis : most were severely asphyxiated or feeble at birth ; eight had intracranial haemorrhage ; all who presented no other reason for persistent atelectasis were premature and puny. The obstetrical records revealed one case of Caesarian section ; two forceps deliveries, one by the breech ; two dry labours ; one case of hydramnios ; and five cases of toxæmia of pregnancy.

Massive pulmonary haemorrhage.—In all types of neonatal pneumonia some amount of haemorrhage is common, depending either upon the intensity of the inflammatory reaction or upon accompanying asphyxial congestion. But there was a group of cases in which haemorrhage appeared to be the primary event, the inflammatory reaction developing secondarily in tissue devitalized by haemorrhage. Massive pulmonary haemorrhage is not uncommon in the new-born and may be a cause of death, usually in the first few days of life. It may be so severe that almost the whole of both lungs is consolidated, or it may affect localized patches of varying extent (fig. 6). The cause is obscure. Browne (1921, 1922) called it 'acute haemorrhagic pneumonia' and believed it to be the first stage of an intense inflammatory reaction. Ylppö (1919) ascribed it to bacterial action. Cruickshank (1930) attributed it as a rule to asphyxia, but noted that many babies in whom it occurred were born of toxæmic mothers. It was seen many times during the present investigation, sometimes associated with infective conditions but more often without any evidence of infection. Usually it was not accompanied by an inflammatory reaction in the lungs. The haemorrhage, however, causes devitalization of the lung tissue by arresting or impairing the circulation. Bacterial infection may then gain access to the devitalized part and set up an inflammatory reaction. This, in the present series, was always slight and confined to small areas of necrotic tissue among much more widespread haemorrhage.

There were thirteen examples of this lesion. Nine of the babies died in the first week, seven in the first three days. Seven were premature. Seven had intracranial haemorrhage, usually subarachnoid or intraventricular. In four of the younger babies there was severe birth asphyxia. One child had multiple haemorrhages. In only one was there evidence of any infective condition apart from the lungs (peritonitis). Two mothers had toxæmia of pregnancy. Bacteriological examinations were made in nine cases. The results were

negative in two and inconclusive in four ; three yielded non-haemolytic streptococci, accompanied by *b. coli* in two.

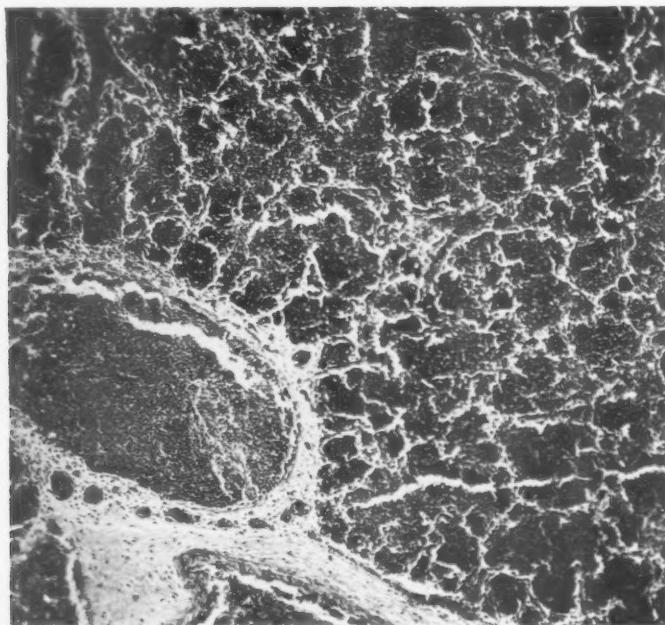


FIG. 6.—Lung of infant three days old. Massive pulmonary haemorrhage filling bronchus and alveoli ; no pneumonia. H. and E. $\times 70$.

Discussion

In this series of cases pneumonia in dead-born infants and in those who survived birth not more than twelve hours was invariably associated with aspiration of an excessive quantity of liquor amnii, with or without meconium, into the lungs ; and in a large proportion of the live-born infants who died within three or four days of birth the same condition was present. This means that in all cases in which the pneumonia certainly developed before birth, and in most cases in which it may have done so, excessive aspiration of amniotic sac contents had occurred, and it suggests that the inflammatory reaction in the lungs depended on the presence of aspirated material.

The fact that bacteriological investigation of cases of this type often gave negative or inconclusive results suggests that the presence of bacteria may not be the only cause of the inflammatory reaction, and that the irritant may be chemical or mechanical and present in the liquor amnii itself. It is not implied that liquor amnii is always capable of producing an irritant effect ; that is quite evidently not the case. But the evidence does suggest that some cases of pneumonia may be due to irritating constituents of the liquor amnii. Various workers (Johnson and Meyer, 1925 ; Helwig, 1933 ; Warwick, 1934) have suggested that liquor amnii, or some of its constituents, may sometimes act as an irritant especially when there is meconium in it. In this series the only case in a dead-born infant in which satisfactory evidence of bacterial

infection was obtained was one with a history of a long dry labour terminated by forceps delivery, in which infection of the contents of the uterus was probable. It would be unjustifiable to draw dogmatic conclusions from the evidence derived from this investigation, but some of the cases are difficult to explain except on the assumption that the inflammatory reaction in the lungs was caused by a non-bacterial irritant in the aspirated material.

In the case of live-born infants it may be impossible to determine if bacterial infection, when proved to be present, took place before or after birth. In certain cases there was no sufficient evidence of any bacterial infection, and in the case of infants who lived a day or two bacterial infection, when found, might have been received after birth.

Pneumonia due to a non-bacterial irritant is unlikely to be severe or progressive. It is noteworthy that in all cases with advanced consolidation bacteria were proved to be present. It is of interest also that in those cases in which it seemed certain that the pneumonia was due to prenatal bacterial infection there was usually a history of some condition that rendered such an event probable, e.g. a long dry labour or gross infection of the liquor amnii ; and such cases presented more definite evidence of septic aspiration than the rest.

The conclusion arrived at from the study of all the cases, in dead-born and live-born, in which there was evidence of prenatal aspiration, was that bacterial infection before birth is not common, but when it does occur it has disastrous consequences for the child ; that a certain number of cases of pneumonia with prenatal aspiration may be caused by a non-bacterial irritant in the aspirated material ; and that the conditions produced in the lungs by aspiration, and by the accompanying effects of asphyxia, are favourable to bacterial invasion after birth.

The cases of pneumonia associated with atelectasis had certain features in which they closely resembled those with prenatal aspiration, although direct evidence of the presence of amniotic fluid in the lungs was lacking. In both groups the lungs were deficiently expanded, poorly ventilated, congested and water-logged. In both the pneumonia had similar characters. As regards the bacteriological findings also the two groups were similar : the bacteria most often associated with both types were low-grade organisms, such as the non-haemolytic streptococci and coliform bacilli, rather than the more commonly recognized virulent pathogens, such as *streptococcus haemolyticus*, *pneumococcus* and *b. influenzae*.

None of the cases with atelectasis presented any direct evidence of prenatal infection, although in some of them there were circumstances that rendered such an event not improbable. As all the babies lived more than twenty-four hours, there could be no certainty that infection had been received before birth, and in the case of those who lived several days postnatal infection was more probable. It would appear therefore that the special characters of the pneumonia in these two groups are determined by the state of the lungs in which the inflammatory reaction develops, especially the presence of oedema and atelectasis. And this state, whether occasioned by prenatal aspiration or due to another cause, offers a peculiarly favourable nidus in the lungs for the settle-

ment and growth of bacteria, no matter whether these are introduced by aspiration before delivery or by inhalation thereafter. It follows that if the occurrence of these conditions could be avoided many of the cases of pneumonia that fall into these two groups could be prevented.

It has already been explained that the available evidence justifies the opinion that excessive aspiration of liquor amnii or material from the vagina is caused by foetal asphyxia, which occasions premature and excessively vigorous respiratory efforts on the part of the unborn child. All cases of pneumonia with prenatal aspiration may therefore be attributed directly or indirectly to foetal asphyxia. Persistent atelectasis without prenatal aspiration may have various causes, but of these probably the most important is severe asphyxia, with resultant depression of the respiratory centre.

Henderson (1931) showed that beyond a certain point asphyxia produces a depressant or even a paralyzing effect on the respiratory centre. Many infants suffer during birth from asphyxia severe enough to produce a depressant effect and difficulty is experienced in establishing respiration. Moreover, the respiratory centre may continue to be in a state of subnormal activity for some time, so that respiration is feeble and full expansion and aeration of the lungs do not take place. Under these conditions there develops in the lungs a state of congestion, oedema and under-ventilation, which is peculiarly favourable to the development of pneumonia. Cruickshank (1930) laid great emphasis upon the importance of atelectasis as a factor predisposing to pneumonia in the new-born. Henderson went so far as to assert that if effective steps were taken to ensure complete expansion of the lungs as soon as possible after birth, neonatal pneumonia would be largely eliminated.

Facts observed in the course of this investigation left no room for doubt that atelectasis and the congestion and oedema associated with it were of the utmost importance in predisposing to the onset of pneumonia and determining its spread. The results of this study thus fully support the view advanced by Cruickshank and Henderson that, if respiratory depression resulting from asphyxia could be prevented or effectively treated, many infant lives could be saved that at present are lost from persistent atelectasis and from pneumonia developing as a sequel to it.

Conclusions

From this study of the types of pneumonia most prevalent in the dead-born and in the early days of postnatal life (those associated with prenatal aspiration and those with atelectasis, which together accounted for nearly all the cases that were fatal in the first three days) one fact that emerges unmistakably is the outstanding importance of asphyxia of the child as a causative factor. It is asphyxia that causes excessive aspiration of amniotic sac contents or vaginal secretion and therefore underlies nearly all cases of true congenital pneumonia. It is asphyxia that produces the pulmonary congestion and oedema, and sometimes the haemorrhage, that afford so favourable a medium for the proliferation of bacteria introduced either before or after delivery. It is asphyxia that causes

the depression of the respiratory centre to which persistent atelectasis with all its attendant dangers is most often due.

It may be doubted if it is sufficiently clearly and universally recognized what risks to the child are incurred when asphyxia during birth is permitted to develop beyond the moderate degree that is harmless and inevitable ; and if the question of prompt and effective treatment designed to prevent its persistent or delayed effects has been given the full attention it deserves in view of its extreme importance to the preservation of infant life.

Summary

The results of a pathological and bacteriological investigation of 177 cases of pneumonia in infants who were born dead or died within twenty-eight days of birth are presented. Pneumonia occurred in 32·7 per cent. of 541 necropsies on such infants. A classification of types of neonatal pneumonia according to the chief pathological characters is given. The pathological characters and pathogenesis of the types of pneumonia that occur in the dead-born and in those who die in the first few days of life are discussed. The importance of asphyxia as a factor in the production of these types of pneumonia is emphasized.

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PART II

When pneumonia develops more than two or three days after birth, it may be attributed in most instances to postnatal infection. Such cases fall into two distinct groups : postnatal respiratory tract infections, which, in the classification given in the previous paper (part I) formed group 3 under the title 'bronchopneumonia and allied types'; and septicaemic cases with lung lesions.

1. Postnatal respiratory tract infections.—Among the eighty-two cases that formed this group the majority had the characters of typical bronchopneumonia (fifty-five cases), whilst some had special features associated with special types of bacterial infection (sixteen cases). There was also a small

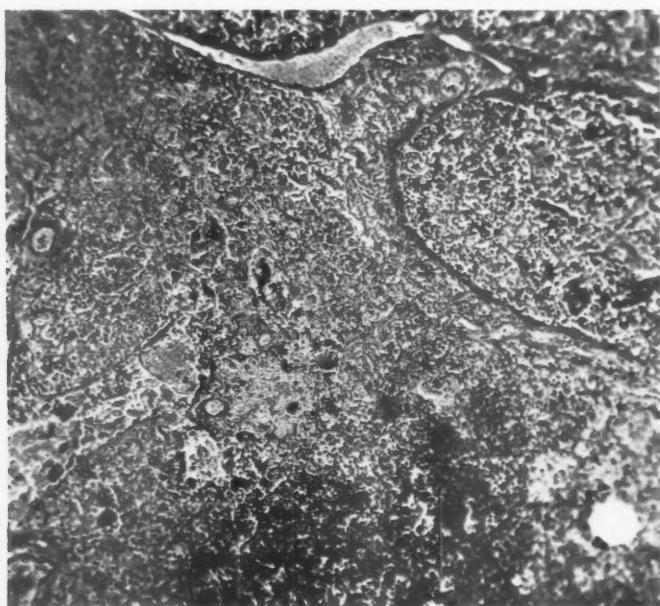


FIG. 1.—Lung of infant ten days old. Pneumonia due to aspiration of stomach contents : foreign matter in bronchus ; haemorrhage, necrosis and consolidation of lung substance. H. and E. $\times 70$.

group (eight cases) in which pneumonia had resulted from septic aspiration after birth and isolated examples of bronchitis without pneumonia (one case) and terminal hypostatic pneumonia (two cases) to which no further reference need be made.

SEPTIC ASPIRATION AFTER BIRTH.—In most of these eight cases the foreign material found in the lungs was milk curd or gastric contents. In one case, in which the child developed acute intestinal obstruction from volvulus, the lungs and air passages were full of meconium which had been vomited. There was a history of vomiting in three other cases. The lungs lesion in all these cases was extensive and of a grave type, with haemorrhage and suppuration (fig. 1). Bacteriological examinations revealed mixed infections, always heavy.

The liability of new-born infants to this type of pneumonia is probably to be explained by their tendency to regurgitate stomach contents and the risk that these may enter the trachea if the child is lying in an unsuitable position.

TYPICAL BRONCHOPNEUMONIA, of which there were fifty-five cases, was the largest pathological group. It is necessary at this point to define what is meant by 'typical bronchopneumonia.' Most of the types of pneumonia considered hitherto in these studies (e.g. that caused by aspiration and that associated with atelectasis) are forms of bronchopneumonia, but in some respects atypical because of the mode of infection or the conditions obtaining in the affected lungs. The cases now to be considered were different in certain particulars and bore a closer resemblance to bronchopneumonia as it is commonly seen in older infants and children as a result of air-borne infection.

In a study of pneumonia in childhood McNeil, Macgregor and Alexander (1929) gave a description of the pathological changes in the lungs in bronchopneumonia, and emphasized certain features of the process which they regarded as distinctive and essential. The chief among these is bronchitis, which is the initial lesion. This is an intense inflammation involving the whole bronchial wall and its lymphatic plexus, and produces, in addition to catarrh, an interstitial inflammation, indicated by swelling and inflammatory cell infiltration, which varies in severity in different cases, but is always present in some degree. The spread of the inflammation to the alveoli is in part a direct spread along the lumen of the bronchus to its terminal expansions and in part peribronchial, through the thickness of the wall to immediately adjacent alveoli which are not in communication with the lumen. This interstitial inflammation with lymphangitis was regarded by these workers as 'a constant feature of all forms of true bronchopneumonia and . . . of the very essence of the pathological process.' Holt and McIntosh (1933) also considered interstitial inflammation to be an essential feature of true bronchopneumonia, and Chase (1935) regarded it as an important point of distinction between cases in which pneumonia in the new-born followed extra-uterine upper respiratory tract infection (i.e. true or typical bronchopneumonia), and those in which it was caused by direct aspiration.

In the selection of cases for inclusion in the group of typical bronchopneumonia the features that were regarded as essential were : (1) bronchitis severe enough to produce not merely superficial catarrh but some amount of interstitial inflammation of the bronchial walls ; (2) a strictly bronchial and peribronchial distribution of the pneumonia ; and (3) absence of evidence of aspiration of foreign material into the lungs (fig. 2).

The ages of children in this group ranged from thirty hours to twenty-eight days. Only four were under four days old, after which age cases were frequent throughout the rest of the month. Typical bronchopneumonia was responsible for only a very few cases in the first three days of life, but from the fourth day onward it was much the commonest type.

In most cases consolidation was moderate or extensive and usually affected both lungs. Some confluence of pneumonic patches was usual, sometimes involving a whole lobe or more in one or both lungs, and being as a rule of greatest extent in the lower lobes. Microscopic examination showed that the exudate was cellular, rich in polymorphs and often accompanied by a large

amount of oedema, haemorrhage and collapse of unfilled alveoli. Bronchi formed the centres of consolidated patches and showed the inflammatory changes already indicated. Suppuration occurred in three cases, originating in bronchi. Pleurisy was found in only three cases.

In this group twenty-five of the babies were premature. Only a small minority had other pathological conditions unconnected with the pneumonia. A considerable number, however, had stomatitis. The proportion of abnormal labours was not high and obstetrical difficulties and complications appeared to have no bearing on the development of pneumonia in the children.

Bacteriological examinations were carried out in forty-seven cases, with

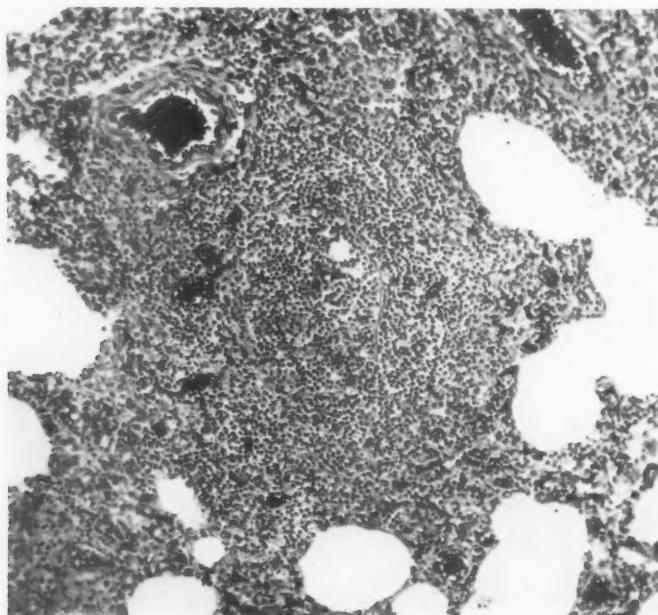


FIG. 2.—Lung of infant twenty-five days old. Typical bronchopneumonia : central bronchus filled with exudate and obscured by inflammatory infiltration ; consolidation of related alveoli. H. and E. $\times 80$.

nine inconclusive and thirty-eight positive results. Pneumococci were isolated from six cases, always accompanied by other organisms, most often *b. influenzae*. *Streptococcus haemolyticus* occurred in five cases, alone in three, *streptococcus viridans* in two ; indifferent streptococci in nine, usually in association with other organisms ; *b. influenzae* in eight, alone once ; and bacilli of the *b. coli* group in sixteen, alone in nine.

The cases of this group may be regarded as representing the common form of pneumonia in the new-born that results from postnatal air-borne infection. That this was the mode of origin is suggested by their resemblance to cases known to be so caused in older infants and by the age incidence of the type in the present series. It is true that in the youngest infants in the group a birth infection was possible, though without evidence either from the pathological study or from the clinical history ; but there was no case which might not have

developed entirely after birth. No well-developed case was seen before the fourth day. For reasons that will be given later, the writer is not of opinion that the frequency of infections with coliform bacilli means a corresponding frequency of infection acquired before delivery.

STAPHYLOCOCCAL PNEUMONIA.—Pneumonia due to infection with staphylococci (other than haematogenous infection) is a type of bronchopneumonia, but, as seen in the course of this investigation, it had features so constant and distinctive that it is convenient to place such cases in a group by themselves. In the present series there were ten cases, excluding one referred to in the previous paper in which grossly infected liquor amnii was the source of infection.

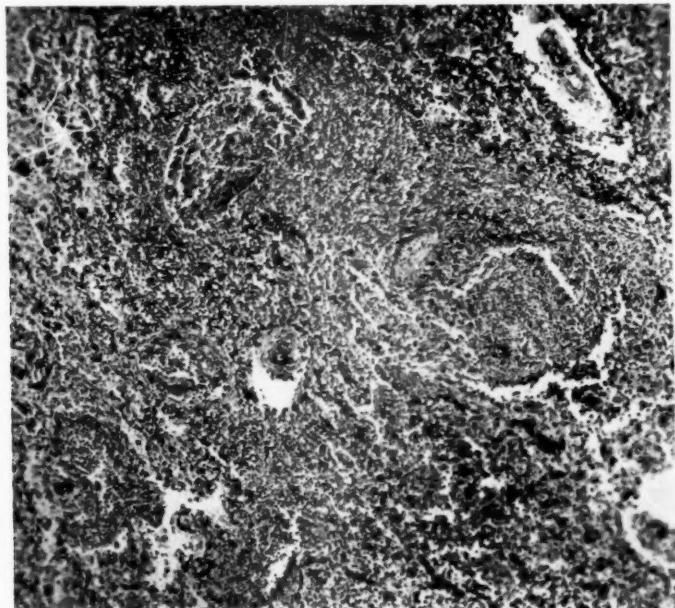


FIG. 3.—Lung of infant eighteen days old. Staphylococcal pneumonia : suppuration destroying bronchi and spreading widely. H. and E. $\times 50$.

The ages of the infants ranged from four to twenty-three days, five being in the first week.

All these cases presented similar pathological characters and closely resembled those described in a previous paper (Macgregor, 1936). In every case pleurisy was present, with an effusion of turbid, blood-stained fluid and purulent or fibrinous exudate. Pneumonia occurred in one or more rather sharply defined patches of massive consolidation, always intensely haemorrhagic, and showing suppuration in the form of ramifying pus-filled cavities (fig. 3). Other parts of the lungs were usually free from pneumonia and there was no generalized bronchitis. Only in one case, in which there was a mixed infection, was there pneumonic consolidation in parts that did not present the appearance described. Microscopic examination showed that the consolidation was due to a combination of massive haemorrhage and inflammatory exudation with a strong tendency to rapid suppuration, which began in the bronchi and spread

into adjacent alveoli, so that abscess cavities were formed and extended in ramifying fashion along the bronchi and along infected lymph vessels. In no case was any evidence found of aspiration of foreign material into the lungs. There was nothing relevant in the maternal histories. Seven of the babies were premature. In no case was there any associated condition likely to have been the source of a generalized blood infection, and no case presented any metastatic lesions. One baby was believed to have been infected from another who shared an incubator and who had a staphylococcal stomatitis. In all cases *staphylococcus aureus* was isolated from the lungs. In nine the staphylococcal infection appeared to be pure; in one *b. coli communis* was isolated from a consolidated area that did not show the appearance of staphylococcal pneumonia, and *staphylococcus aureus* from the characteristically affected part. This type of pneumonia is due to an infection that enters the lungs by the bronchi. Some of its features, particularly its localization and the heaviness of the bacterial infection, suggest that it may be caused by aspiration of grossly infected foreign matter. Johnson and Meyer (1925) thought that staphylococcal infection of the lungs might be caused by aspiration of milk. In the present series there was no evidence obtainable either from the history or from the pathological examination, to suggest any such occurrence or aspiration of any other foreign matter.

PNEUMOCOCCAL ALVEOLAR PNEUMONIA.—Holt and McIntosh (1933) described a type of pneumonia in young infants in which the patches bear no relation to bronchi and interstitial inflammation is absent, and which they distinguished from bronchopneumonia under the name of 'lobular pneumonia.' In the present series there was a small group of six cases to which this description could be applied. The children's ages ranged from three to twenty-seven days, all but the youngest being over ten days old. The pneumonia occurred in well-expanded lungs. The consolidation was patchy, the patches being of variable size and often large. Within the patch consolidation was complete and uniform, so that the affected part stood out above the level of adjacent aerated substance, a feature seldom noted in bronchopneumonia owing to associated secondary collapse. The patches were sharply defined, often having a clear, straight margin. They were uniform in colour and consistence, and on section presented a drier surface than in typical bronchopneumonia, the appearance, but for the patchy distribution, being reminiscent of lobar pneumonia at the stage of red hepatization. Pleurisy was not present in any case. Microscopically the pneumonic areas showed complete and uniform consolidation, all the alveoli being fully expanded and filled with cellular exudate. The bronchi contained exudate similar to that in the alveoli and shared in the general congestion, but otherwise showed little inflammatory change (fig. 4). The sharply defined margins of the consolidated areas were due to their being bounded by interlobular septa, and beyond the boundary of the patch the lung substance was fully aerated and did not show either bronchitis or outlying patches of consolidation related to bronchi. There was no true bronchitis or interstitial inflammation. The consolidation had not a strict bronchial or peribronchial distribution, but occurred in lobules or groups of lobules. These features

of the pathological process separated them from the group of typical bronchopneumonia.

Bacteriological investigation resulted in the isolation from each case of a pneumococcus in pure culture : Type I in two cases ; Type II in three cases ; Type III in one case. The particular type of pathological process exemplified by these cases is thus apparently characteristic of pneumococcal pneumonia in the new-born. The term 'alveolar pneumonia' is suggested as a suitable designation for this type. This name was applied by McNeil, Macgregor and Alexander (1929) to pneumonia of the lobar or croupous type in children, in whom it is often not of lobar extent. It indicates that the inflammation

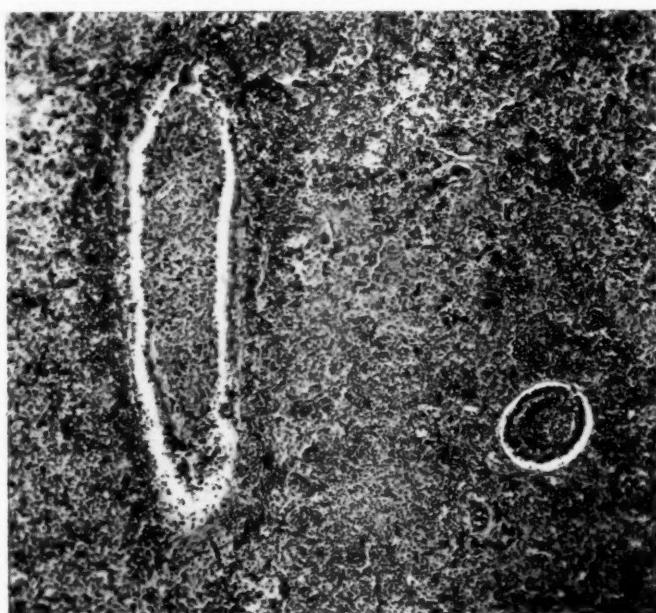


FIG. 4.—Lung of infant twelve days old. Pneumococcal alveolar pneumonia : uniform complete alveolar consolidation ; bronchial walls undamaged. H. and E. $\times 65$.

is alveolar rather than bronchial, and avoids reference to the gross distribution and extent of consolidation. It is preferable to 'lobular,' as common usage has made that term almost synonymous with 'bronchopneumonia.' It has the further advantage that it indicates the essential identity of this type of pneumonia in the new-born with the better known and more typical forms of pneumococcal pneumonia in older children and adults.

2. Haematogenous infections of the lungs.—In a group of eighteen cases the inflammatory changes in the lungs were part of a generalized septic infection that originated elsewhere, and were due to blood-spread infection. The lung lesions in nine cases took the form of septic infarcts or pyaemic abscesses, accompanied by septic pleurisy with purulent or sero-fibrinous effusion. In three cases of haemolytic streptococcal infection the lungs contained focal areas of consolidation, unrelated to bronchi and having the scattered distribution of embolic lesions, but without suppuration.

In six cases the lesion was a septic pleurisy followed by secondary invasion of the lungs by means of a septic lymphangitis, which sometimes went on to suppuration. The ages of the babies ranged from four to twenty-two days, all but one being under one week. The pleurisy took the form of a viscid purulent exudate, usually scanty, without fibrin. Involvement of the lungs was often not detectable at necropsy, but sometimes slight consolidation was suspected, and in one case small subpleural abscesses were visible. Purulent exudate was found microscopically in dilated lymph vessels, both those of the pleural plexus and those of the deep perivascular plexus throughout the lungs (fig. 5 and 6). In some cases inflammatory infiltration of the septa and perivascular



FIG. 5.—Lung of infant twenty-two days old. Septic lymphangitis following pleurisy : pleural lymph vessel distended with pus. H. and E. $\times 60$.

tissue and consolidation of adjoining alveoli were found. In several, abscesses had developed under the pleura or in interlobular septa. In all these cases the inflammatory changes in the lungs were entirely dependent on and secondary to the pleurisy. In the writer's experience this particular pathological process occurs only in very young infants. In older subjects there is little tendency for an infection of the pleura to invade the lung along the lymph vessels ; this is prevented by valves which are situated at the junction of the pleural and septal lymphatics and open towards the pleura (Miller, 1919 and 1936). The fact that lymph-borne infection can pass so much more readily inward from pleura to lung in the new-born suggests that the development of these valves is incomplete until a little time after birth. Miller was able to produce some evidence to show that this is the case.

In the whole group of haematogenous infections, six of the eighteen babies were premature. The ages ranged from four to twenty-eight days, eight being under a week old. Pleurisy with lymphangitis was commoner in the younger children, pyaemia or septic infarction after the first week. The primary focus of infection was established in ten cases in which infection was received after birth : umbilical sepsis in four, septic dermatitis in five, and otitis media in one. In one case the history strongly suggested intra-uterine transplacental infection. The mother had haemolytic streptococcal septicaemia before parturition ; the baby died on the fourth day with haemolytic streptococcal septicaemia and pleurisy. This was the only case in the whole series in which any really suggestive evidence of transplacental infection was found. In the

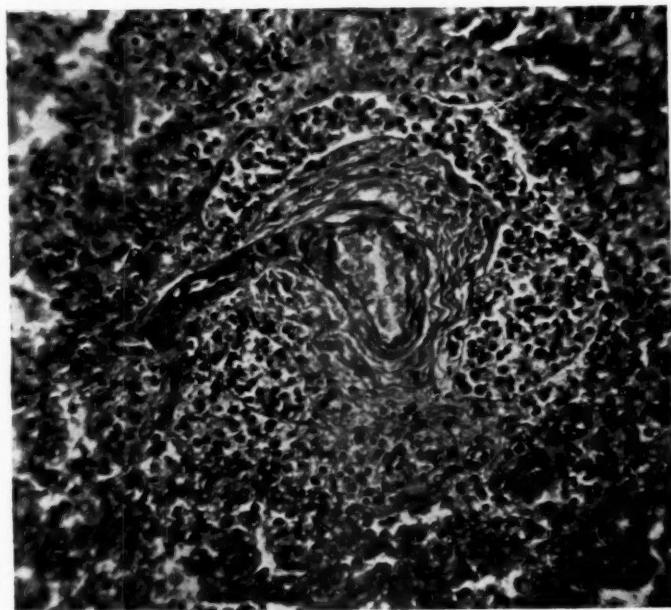


FIG. 6.—Lung of infant four days old. Septic lymphangitis following pleurisy : deep perivascular lymph vessels distended with pus. H. and E. $\times 180$.

remaining cases the source of infection and its primary site were obscure. Associated metastatic lesions in other parts of the body were found as follows : meningitis, five cases ; abscesses in kidneys, two cases ; endocarditis and myocardial abscess, each one case.

Bacteriological examinations were made in all eighteen cases and in each resulted in the isolation of a single type of organism in pure culture : streptococcus haemolyticus in five ; streptococcus viridans in one ; staphylococcus aureus in six ; coliform bacilli in six. Blood cultures were made in eleven cases and in nine produced growths of the same organisms as were obtained from the lungs, but in two were spoiled by post-mortem contaminants.

Summary of the bacteriological study

Bacteriological examinations were carried out in 150 cases in which inflammatory changes were found in the lungs. Positive results that were regarded as significant were obtained in 106 cases. The frequency of occurrence of the various organisms and their relation to the patient's age at death and to the pathological type of pneumonia are summarized in tables 1 and 2. The types of bacteria that were frequently found included several species that commonly cause pneumonia in older people (haemolytic streptococci, pneumococci, *b. influenzae*). These were associated principally with those types of pneumonia that result from postnatal infection (bronchopneumonia and allied types, and—in the case of *streptococcus haemolyticus*—septicaemic infections), and occurred more often in the later part of the neonatal period than in the earlier

TABLE 1
BACTERIOLOGY IN RELATION TO AGE AT DEATH

ORGANISM	AGE IN DAYS					
	STILL-BORN	0-3	4-7	8-14	15-21	22-28
<i>Streptococcus haemolyticus</i> ...	—	1	1	1	3	7
<i>Streptococcus viridans</i> ...	—	5	1	—	1	1
Indifferent streptococci ...	—	9	2	7	3	—
<i>Staphylococcus aureus</i> ...	—	2	9	4	3	1
<i>Pneumococcus</i> ...	—	1	—	2	3	6
<i>B. influenzae</i> ...	—	1	—	1	1	5
<i>B. coli group</i> ...	1	9	9	15	8	1
<i>Neisserian diplococci</i> ...	—	—	—	2	—	5

TABLE 2
BACTERIOLOGY IN RELATION TO PATHOLOGICAL TYPE OF PNEUMONIA

TYPE OF PNEUMONIA	ORGANISM						
	STREPTOCOCCUS HAEMOLYTICUS	STREPTOCOCCUS VIRIDANS	INDIFFERENT STREPTOCOCCI	STAPHYLOCOCCUS AUREUS	PNEUMOCOCUS	<i>B. INFLUENZAE</i>	<i>B. COLI GROUP</i>
Prenatal aspiration ...	—	3	5	1	—	1	6
Atelectasis ...	2	2	3	1	—	—	4
Haemorrhage ...	—	3	—	—	—	—	2
Postnatal aspiration ...	—	—	—	—	—	—	5
Bronchopneumonia and bronchitis ...	6	2	10	1	6	8	19
Staphylococcal pneumonia ...	—	—	—	10	—	—	1
Alveolar pneumonia ...	5	1	—	6	6	—	6
Haematogenous lesions ...	—	—	—	—	—	—	—

days. There were also several species that are less often a cause of pneumonia in older subjects (streptococci of viridans and indifferent types and the *b. coli* group). These were the usual cause of the types of pneumonia that are peculiar to the neonatal period, and they occurred with great frequency in the earliest days of life. The *b. coli* group, however, caused all types of pneumonia (except those specifically associated with staphylococci and pneumococci) and were particularly common in typical bronchopneumonia. Staphylococcal infections were usually postnatal, but occurred early in the neonatal period. Some interesting considerations that arise from these facts are discussed below.

Discussion

From the point of view of prevention these cases in which infection is received after birth are of the first importance. Whether a case belongs to the respiratory or to the haematogenous group, infection received after birth is infection received from the child's environment and is therefore capable of being checked or controlled at the source. Of all the types of pulmonary infection studied during this investigation, those attributable to postnatal respiratory tract infection formed the largest group, and in the great majority of these cases pneumonia was the direct cause of death. It is undoubtedly in this group that the largest number of deaths from pneumonia could be prevented.

One of the most interesting facts revealed by the investigation of these cases of postnatal infection was the frequent appearance, as causative organisms, of types of bacteria that seldom appear in a similar rôle in older subjects. The most conspicuous example of this was the group of coliform bacilli. It must be explained that stringent precautions were taken to exclude the fallacy of post-mortem and terminal invasions of the body by intestinal bacteria, which undoubtedly takes place often and rapidly in new-born infants. No case was regarded as being due to infection with *b. coli* unless (a) films of lung juice and sections of pneumonic lung showed profuse phagocytosis of the bacilli by cells in the exudate (fig. 7 and 8), and (b) the distribution of the pneumonic areas in sections of the lungs corresponded to that of the bacilli. It was considered that the strict application of this rule excluded all reasonable possibility of mistaking post-mortem or terminal invaders of the tissues for genuine pathogens. In particular, the amount of phagocytosis found in many cases was so remarkable that it could not be doubted that the bacilli represented an ante-mortem infection. When any reasonable doubt existed the result was regarded as inconclusive and set aside.

Browne (1921 and 1922) considered that the frequency of *b. coli* in neonatal pneumonia was proof of the importance of infection before or during birth. But this investigation showed that *b. coli* infection occurred not only in cases in which prenatal infection was probable or possible, but even more often in older babies in whom infection before delivery was improbable or impossible and that it was most often associated with pneumonia of a type that is much more likely to be caused by air-borne or droplet infection than by aspiration. The most frequent appearances of organisms of the *b. coli*

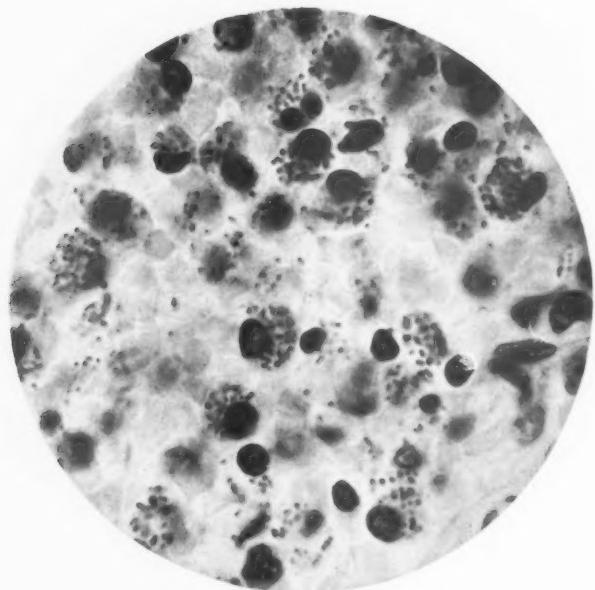


FIG. 7.—Lung of infant four days old. Case of *b. coli* bronchopneumonia : profuse phagocytosis of bacilli by cells in exudate. H. and E. $\times 900$.

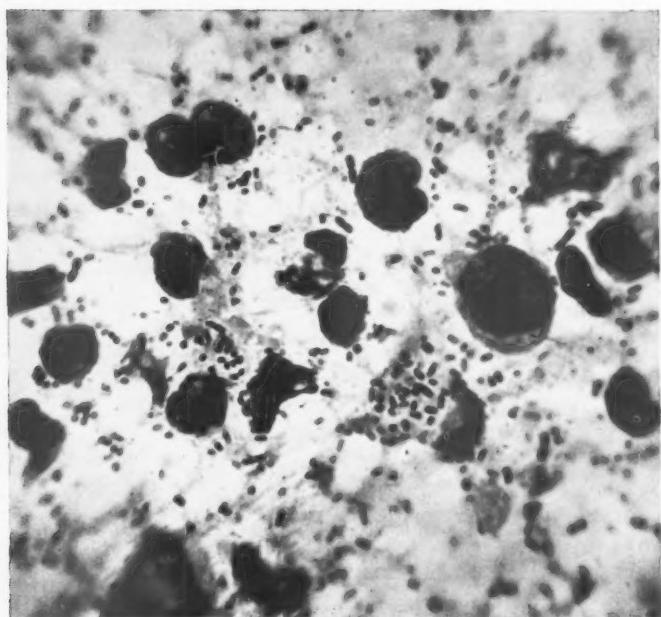


FIG. 8.—Film of exudate from lung. Case of *b. coli* bronchopneumonia : cells containing many ingested bacilli. Gram's stain. $\times 1100$.

group were in cases of typical bronchopneumonia in babies more than a week old. They appeared also as a not infrequent cause of septicaemia in cases without evidence of prenatal aspiration. This matter is important because pneumonia due to coliform bacilli (other than the bacillus of Friedländer) seems to be peculiar to the neonatal period. In this series its prevalence ended at the end of the third week of life. The writer has made many bacteriological examinations in cases of pneumonia in infants and children and has never seen one caused by any member of the colon bacillus group after the first month of life. Yet during the first three weeks they are among the commonest of all bacteria associated with pneumonia. This is a remarkable fact and seems to indicate the existence of a special susceptibility in the new-born to infection by these organisms.

In the literature a considerable body of evidence suggests this special susceptibility, with reference not only to pneumonia but also to general sepsis and meningitis. Whereas septicaemia due to *b. coli* and related organisms is recognized to be rare in older persons, numerous authors have commented on its frequency or reported cases in the new-born (Ylppö, 1919; Cruickshank, 1930; Dunham, 1933; Park and Williams, 1934; Merritt and Paige, 1935; Butler, 1937). Meningitis due to these organisms has been frequently reported in the new-born (Ylppö, 1919; Cook and Bell, 1922; Neal, 1924; Cruickshank, 1930; Park and Williams, 1934; Craig, 1936; Mulhern and Seelye, 1936; Crockford, 1938), though similar cases in older subjects are very rare. There is therefore a good case for the contention that new-born babies are peculiarly susceptible to infection with these organisms.

Various suggestions have been offered to explain the frequency of *b. coli* infection in the new-born: undue absorption of bacteria from the bowel (Cook and Bell, 1922; Ylppö, 1919); an absence of 'normal' agglutinins for these organisms in the blood (Cook and Bell, 1922; Park and Williams, 1934; Zinsser and Bayne-Jones, 1934); and inadequate inflammatory reaction to bacterial invasion, manifested by a lack of polymorphonuclear leucocytes in the exudate (Ylppö, 1919; Browne, 1921 and 1922; Gordon and Lederer, 1928; Müller and Bayer, 1934).

The first of these suggested explanations may meet some cases of septicaemia of obscure origin, but hardly suffices for pneumonia of the primary type. The second is of doubtful accuracy, and, in view of the results of immunological studies of the *b. coli* group (Mackie, quoted by Muir and Ritchie, 1932), it may be doubted whether, even in older subjects, humoral antibodies provide any substantial protection against these organisms. The third is entirely at variance with the writer's experience. It is possible that the explanation of the special susceptibility of the new-born may be found to lie in the direction of local tissue immunity. It may be suggested that the mucous membranes of the alimentary and respiratory tracts acquire a local immunity against organisms of the *b. coli* group through constant or repeated contact with them, and so resist invasion by them, except perhaps in small and harmless numbers; and that this immunity is absent, or incomplete, at birth, and is gradually acquired during the first weeks of life. There would thus be a period immediately following birth, when these organisms first enter the body of the child and for a time thereafter, when there is a greater risk of virulent invasion of the blood and

tissues. Applied to the intestinal mucous membrane, this may explain some of the cases of *b. coli* septicaemia for which no obvious source is found, but no doubt in the case of the intestine, where colon bacilli must inevitably, speedily and numerously arrive soon after birth, any early tendency to virulent invasion must soon be overcome. In the case of the respiratory tract, where they are not regularly present, though their appearance is by no means rare (Gundel and Schwartz, 1931-32), the tendency to virulent invasion is probably greater and more prolonged. Moreover, it may well be greater in the case of premature infants.

Nor is it only with regard to colon bacillus infections that a special susceptibility in the new-born is manifested. Staphylococcal pneumonia is another interesting example. It is not confined to the neonatal period, or even to childhood, but is rare in older persons, whereas it is comparatively common in the new-born. Moreover, in most cases in adults the invasion of the lungs by staphylococci is preceded by infection of some other kind, most often influenza, as if the staphylococci are ordinarily incapable of virulent invasion of a healthy respiratory tract and become dangerous only when the mucous membrane has been rendered vulnerable by a preceding infection. In the very young the staphylococcal infection is in most cases primary and pure ; the staphylococci can exert their full pathogenic action on the respiratory tract without the help of any antecedent or coincident infection of another kind.

The results of this investigation of postnatal infection point clearly to one conclusion of great importance : the vital need for the most scrupulous attention in every detail to hygienic measures directed towards guarding the new-born against exposure to infection, especially infection of the respiratory tract, and the necessity that those who have charge of them should clearly appreciate the extent of the risk against which they must be protected. All are agreed that new-born babies must not be exposed to infection by contact with persons who are harbouring known pathogenic bacteria, but it is not so fully understood that organisms that are common and harmless commensals in the mouth, nose or pharynx of older people are potentially dangerous pathogens to the new-born.

It follows that young infants should be handled and fondled as little as may be by older persons ; that crowded conditions, in which the bacterial content of the atmosphere is bound to be high, are dangerous to them ; and that attention to the hygiene of the baby's mouth and nose, and of the mother's breast when she suckles her child cannot be too careful. This has a bearing on the care of new-born babies in their own homes. It applies with equal or even greater cogency to the practice of infant hygiene in maternity hospitals, where, if conditions fall short of the best attainable, the babies may be exposed to risks that are not always fully realized. It is clearly undesirable that they should spend more time than that needed for suckling in the adult wards, especially if these contain a number of patients, when an atmosphere too rich in bacteria to be suitable for young infants can hardly be avoided. It is also inadvisable that the nurses in charge of the adult wards should at the same time have the care of the babies, because a satisfactory regime of infant hygiene

requires the constant supervision of one who has special experience, and because if nurses have to divide their attention between mothers and babies, there are obvious risks of lapses in technique which may open the way to dangerous infection.

These conclusions received interesting confirmation from a comparison of the records, as regards neonatal pneumonia, of two hospitals. Hospital A was old and overcrowded and has now been superseded by a modern hospital. The babies ordinarily shared the adult wards with their mothers and were cared for by the nursing staff of their wards, upon whom devolved at the same time the care of the mothers. The medical and nursing staff thus worked under the disadvantage of conditions that made a satisfactory regime of infant hygiene impossible. Hospital B is modern, well situated, not overcrowded. The babies have their own nursery and go to their mothers' wards only for suckling. There is ample provision for the isolation of any child who develops an infection, and a hygienic regime of a high standard is maintained. The conditions under which the babies lived in the two institutions were thus sufficiently different in certain essential respects to make a comparison of the results obtained both interesting and instructive (table 3).

TABLE 3.
NEONATAL PNEUMONIA IN TWO HOSPITALS (A AND B)

	NUMBER OF CASES		PER CENT. OF ALL PNEUMONIA		PER CENT. OF ALL NECROPSIES	
	A	B	A	B	A	B
Total necropsies	358	118	—	—	—	—
Total pneumonia	117	24	—	—	32.7	20
Pneumonia in first 3 days ...	42	18	36	75	11.7	15.4
Pneumonia in first week ...	68	23	58	96	19	19.5
Pneumonia after first 3 days ...	75	6	64	25	21	5
Pneumonia after first week ...	49	1	42	4	13.7	0.8
Postnatal airborne infection ...	51	2	43.5	8.3	14.2	1.7

The percentage of necropsies in which pneumonia was found was considerably higher in Hospital A than in Hospital B, the figures being 32.7 and 20 per cent. respectively. The contrast is more striking and much more significant when a comparison is made of the pneumonia cases in the two hospitals in respect of age incidence and pathological type. In hospital A many cases occurred after the third day and even after the end of the first week, and cases continued to occur up to the end of the month. In Hospital B few cases occurred after the third day and only one child died with pneumonia after the first week. In Hospital A cases of the types caused by postnatal air-borne or droplet infection (i.e. environmental infection of the respiratory tract) were common (43.5 per cent. of all pneumonia cases and 14 per cent. of all necropsies). In Hospital B the incidence of environmental infection was low—two cases, representing 8 per cent. of all pneumonia and 1.7 per cent. of all necropsies.

It is thus shown that in Hospital A primary pneumonia due to postnatal respiratory tract infection accounted for little less than half of all the pneumonia in the new-born and was responsible for a substantial proportion of the whole death rate. The bacteriological findings showed that the virulent respiratory tract pathogens (*streptococcus haemolyticus*, *pneumococcus*, *b. influenzae*) were of less frequent occurrence than other common organisms (*staphylococci* and the coliform bacilli) which occur as commensals in the mouth and throat, or otherwise about the persons of many healthy people, and might be expected to be more numerously present in the case of adult patients being nursed in bed, and of nurses in attendance on them, and to be present in the atmosphere of their wards. In Hospital B nearly all the pneumonia that occurred among the babies was either associated with birth asphyxia or secondary to lung injury caused by stress of birth or to massive pulmonary haemorrhage ; and in most of these cases the bacteriological results were inconclusive or negative. The two cases in which pneumonia was attributable to postnatal respiratory tract infection were both due to *b. influenzae*. There was no case of primary pneumonia due to *staphylococci* or *b. coli*. But for the two cases mentioned, this hospital was free from fatal postnatal primary respiratory tract infections among the babies for the entire period of four years covered by the investigation.

It is not to be believed that this difference in the incidence of postnatal infection is unconnected with the different conditions under which the babies lived in the two hospitals. The facts revealed by this comparison afford strong support for the argument here presented, and much encouragement may be had from them. For they show that pneumonia in the new-born due to postnatal infection is preventable and can be almost completely eliminated by scrupulous attention to hygienic principles that are already known.

In conclusion, therefore, it may be stated that the prevention of neonatal pneumonia of the types that develop after the first two or three days of life is entirely a problem of hygiene and nursing care. New-born babies must be protected, not only from infection with recognized pathogens, but also from conditions that occasion a too heavy invasion of the respiratory tract by common commensals, of which the most dangerous are *staphylococcus aureus* and organisms of the colon bacillus group. To accomplish this demands a hygienic regime of a high standard. The maintenance of the necessary standard is particularly important in institutions, where otherwise conditions may favour the spread of infection among the many susceptible infants. It can be asserted quite definitely that this type of pneumonia is preventable and could be almost completely abolished if a satisfactory system of neonatal hygiene were universally practised.

Summary

An account is given of the pathological characters and bacteriology of the types of neonatal pneumonia that are attributable to postnatal infection.

The largest group was formed by cases having the characters of typical bronchopneumonia. Cases with special characters associated with staphylococcal and pneumococcal infection are described.

Some peculiarities of haematogenous infections of the lungs in the new-born are discussed.

A summary of the bacteriological study is given. The importance of organisms of the colon bacillus group in neonatal infections is discussed.

A comparison of the incidence of neonatal pneumonia in two hospitals is given.

The conclusion is reached that pneumonia due to environmental infection can be prevented by strict attention to neonatal hygiene.

It is a pleasure to express gratitude to Prof. Charles McNeil, whose unflagging interest in the work was a source of constant encouragement. Thanks are due to the members of the visiting staffs of the Royal Maternity Hospital, the Elsie Inglis Memorial Maternity Hospital and the Royal Hospital for Sick Children, Edinburgh, for the use of clinical records ; to Dr. W. S. Craig and Dr. J. L. Henderson, for help in performing some of the necropsies and in the analysis of clinical records ; and to Mr. Edward Gorton, for technical assistance throughout the investigation.

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CASE REPORTS

CEREBRAL OEDEMA IN SCARLET FEVER

BY

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The literature contains no reference to cerebral oedema as an early complication of scarlet fever. It is likely, therefore, that the condition is extremely rare.

Case history

The patient, a boy aged fifteen years, gave a history of measles and chicken-pox in infancy and of rheumatic fever nine years ago. His mother stated that the present illness started with sore throat, occipito-cervical headache, backache and a temperature of 101·2° F. These symptoms persisted for three days, vomiting occurred once, sordes was obstinate, marked thirst was satiated with abundance of fluids, and, in spite of profuse perspirations daily, the temperature gradually rose to 103·8° F. Early on the fourth day his doctor was called and prescribed sulphonamide ; later on that day a deep red flush appeared on his neck and face. Throughout he had been drowsy, but talked quite sensibly. On the fifth day his condition had definitely improved, his throat was easier, his temperature had dropped two degrees, but as the rash persisted and had spread, he was sent to hospital.

On admission he looked ill, his face sallow and puffy, his cheeks desquamating in large flakes. On his neck was a dusky purplish rash, the unusual colour being due to multiple petechiae, and on the body and limbs a generalized punctate eruption of moderate severity. The palate and tonsils were swollen and brightly injected, the palate having a punctate appearance ; the tonsils were covered by a yellow lacunar exudate which was easily removed. Some viscid mucus covered the mouth and fauces, while the tongue was at the 'white-strawberry' stage. The temperature was 101° F., the pulse of poor tension, pulse rate 100, respirations 20. He was given an intramuscular injection of concentrated and refined streptococcus antitoxin (Parke Davis and Co.), the dose being 9000 units.

On the following morning exfoliation of the mouth and tongue was complete ; the tongue was then a 'red-strawberry', and the tonsils clean and bright red. The rash on the neck was still dusky and showed early desquamation, whilst the body rash had almost gone. The temperature was 97·6° F., the pulse 80.

In spite of the marked improvement in the clinical signs the patient appeared to be dull and listless, but answered unsmilingly in monosyllables when spoken to. Throughout the day he was able to read, or at least he pretended to, but made repeated attempts to get out of bed, occasionally requiring moderate

restraint as he was apparently unable at these times to realize fully what was being said to him or what he was doing. In the evening his condition had deteriorated still further : he was then definitely stuporose.

Examination of the heart, lungs and abdomen was completely negative ; examination of the central nervous system, on the other hand, gave some interesting results. Superficial and deep reflexes were either absent or greatly diminished : the knee-jerks were weak and elicited with difficulty, the plantar responses were faint but definitely flexor, and the abdominal and epigastric reflexes absent. There was no stiffness nor retraction of the neck, Kernig's and Brudzinski's signs were negative, and there was no ankle clonus. There was no photophobia, nor nystagmus ; the pupils were equal and regular with a normal degree of dilatation whilst ophthalmoscopic examination showed clear discs but some dilatation of the retinal veins. In reply to a shouted question he denied headache or pain. His co-operation in this examination was anything but active : his actions those of an automaton with a wooden and expressionless face. His temperature was 97.8° F., his pulse 70 and his respirations 18. The urine was normal in amount and contained no abnormal constituents.

He passed an extremely restless night, with little sleep till seven o'clock in the morning. When seen at ten o'clock on the seventh day of the illness, he was practically comatose, but could still be roused with difficulty. It was found he had had incontinence of urine between the hours of seven and ten. Examination gave the same results as on the previous evening. Lumbar puncture was considered, but his condition had deteriorated to such an extent that urgent treatment rather than leisurely diagnosis became imperative.

His head was lowered, he was given magnesium salts, one ounce by the mouth and one ounce by rectum, followed in a few minutes by castor oil, one ounce with thirty minims of coramine. These measures proving ineffectual, a soap and water enema was administered with a profuse watery result. Within a few minutes he sat up in bed and, looking round with a questioning gaze, engaged the nurse in animated conversation. Examination later in the day revealed normal and brisk reflexes, both superficial and deep, in an intelligent and smiling patient who had no memory of the previous two days.

His progress thereafter was wholly uneventful, his temperature remaining between 97° and 98° F., his pulse 54/60 for the next three days. He was able to get up on the fourteenth day of his stay in hospital, and to leave on the twenty-sixth day. He has remained perfectly fit since his discharge.

Discussion

The patient's condition on the day of admission to hospital was believed to be due to the toxæmia of a severe scarlet fever infection ; on the second day, with a normal temperature and pulse and a clean tongue (strong presumptive evidence that the immediate toxæmia had been overcome), it was thought to reflect an innate dull mentality ; whilst on the third day, in the presence of a gross and progressive deterioration in the mental picture, it became obvious that the cause was then some obscure brain condition.

A normal temperature, bradycardia, marked stupor or even coma, diminution or absence of superficial and deep reflexes, incontinence of urine and dilatation of retinal veins (all signs of some general cerebral irritation), led to the provisional diagnosis of cerebral oedema. Even without lumbar puncture, a procedure of doubtful diagnostic value in a non-inflammatory lesion of recent onset, the differential diagnosis gave rise to no great difficulty, as all the usual

complications of scarlet fever, and causes extraneous to it, could be rapidly excluded.

Serum anaphylaxis was ruled out, as the signs, both in time and type, were wholly inapplicable to such a condition, and as refined and concentrated serum, which reduces the risk of serum shock to a negligible minimum even in a susceptible patient, had been employed.

Meningismus has been said to occur as a rare and fleeting phenomenon at the onset of hypertoxic scarlet fever. It is doubtful if it exists as a clinical entity, and it is likely that the syndrome results from an attack of abortive serous meningitis. Meningitis in all its forms, and its sequelae, could be dismissed in the absence of headache, neck rigidity or retraction, positive Kernig's and Brudzinski's signs, pyrexia and suppurative otitis media. It is generally agreed that practically all cases of meningitis are secondary to infection of the middle ear and are extremely rare before the tenth day.

Uraemia was unlikely as the pupils were not contracted, the discs were clear, there was no headache, vomiting or convulsions, the tongue was clean, the breathing normal and the urine free from albumin with no retention or diminution in amount.

Cerebral oedema is usually represented by an increase in the cerebrospinal fluid, especially in the meshes of the pia, whilst the brain substance may be infiltrated with fluid and the amount of fluid in the ventricles may be increased. The symptoms are generally ill-defined. It is probable that two factors were involved in its production in the case under discussion : (a) toxæmia and (b) water intoxication.

(a) Toxæmia. The toxin in scarlet fever is absorbed into the system and gives rise to the rash and the constitutional symptoms. The rash is produced by dilatation of the skin capillaries, the fragility of walls of which is increased so that minute petechiae may occur in the flexures, or even elsewhere in the more severe case. The severity of the rash may therefore be taken as a true index of the toxicity of the infection and of the damage, potential or actual, to the capillaries in the internal organs. The primary object of treatment is to neutralize this toxin at the earliest possible moment, before it has become fixed or 'etched' in the capillary walls, that is, before the fifth day. No matter at what stage antitoxin is given, if the amount is adequate, it will overcome the immediate toxæmia, that is, it will neutralize the whole of the circulating toxin in a few short hours, but the later the treatment the greater will be the damage to the capillaries.

In the present case, which was of toxic type as was shown by the severity of the constitutional symptoms and the presence of a petechial rash on the neck, antitoxin treatment was not instituted till the fifth day of the illness. Some complications, resulting from direct damage by the toxin itself, was not therefore unexpected. Probably the complication of this type most commonly seen is albuminuria, and it is believed to result from the action of toxin on the vessels of the kidney, especially those of the parenchyma and glomeruli. It would not therefore be unreasonable to suppose that cerebral oedema may occur as evidence of analogous damage to the minute vessels of the brain. The lesion may in

some degree be compared with that in cerebral concussion. Cannon (1901) says that this condition is characterized by the formation of diffuse multiple small thrombi and by the presence of punctate extravasations in the minute capillaries which cause a relative ischaemia of the parts, and that brain substance, like other tissues, when deprived of oxygen, takes up fluid from the circulating media and becomes oedematous.

(b) Water intoxication. This condition may have resulted from excessive water intake following profuse sweats : both these factors were present during the four days before admission to hospital. Helwig, Schutz and Currey (1935) suggest that injudicious forcing of fluids produces an upset in the salt-water balance of the body, or a disturbance in the normal isotonicity of the blood, with a resulting cerebral oedema with intoxication.

The object of treatment was to relieve the water-logged condition of the brain, and incidentally to reduce any increase of intracranial pressure which may have resulted from increase in the amount of fluid in the ventricles, by stimulating its circulation and consequent oxygenation, and by causing depletion of tissue fluids.

Summary

A case of cerebral oedema, occurring in the course of toxic scarlet fever infection, is recorded. The complication was an early one and probably resulted from toxæmia and from water intoxication. The immediate response to simple and appropriate treatment would seem to confirm the diagnosis.

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TRICHOBEZOAR (HAIRBALL) CAUSING ACUTE
INTESTINAL OBSTRUCTION IN A CHILD
AGED THREE YEARS

BY

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Although not uncommon in mental hospital patients, a trichobezoar in a child is not often seen. Besides being rare, the condition is of considerable historical interest. The word 'bezoar,' derived from Arabic 'badzehr' or from Persian 'pad zahr,' signifying counter-poison or antidote, is the term applied to masses found in the intestine and stomach of both men and animals. Bezoars have been known since the twelfth century B.C. They were supposed to have marvellous medicinal and mystical properties ; and this was the belief as late as the eighteenth century A.D., *Tinct. Bezoardio* being included in the *materia medica*. Such was the considered value of bezoar that many counterfeits were made. To offset this trade, elaborate tests, as futile as the bezoar, were formulated to differentiate true from false (Eusterman and Balfour, 1937).

Bezoars which are found in human beings are classified as : trichobezoar (hairball) ; trichophytobezoar (ball of hair and vegetable fibre) ; phytobezoar (ball of vegetable fibre) ; and concretion. The first real case was described by Baudement in 1779 ; and the first reported removal by operation was in 1883 (Schwartzman, 1937).

These foreign bodies may produce no symptoms, but those most commonly found are epigastric pain, nausea, vomiting and diarrhoea. A palpable tumour may be present, and the most important aid in diagnosis, according to Eusterman and Balfour (1937), is the radiological examination. By using barium, a non-opaque foreign-body in the stomach is outlined. When found in children, trichobezoar is usually in the stomach.

Case report

R. C., a male child aged 3½ years was in the hospital on account of a dry skin eruption attributed to the use of an alkaline soap. He had been in the

TRICHOBEOZAR CAUSING INTESTINAL OBSTRUCTION 357

hospital six months before for the same trouble. He was a fair-haired child in rather poor general condition. He was not obviously mentally defective, nor did he pull his hair out. On March 12, 1939, he vomited once, but on examination he showed no signs of illness. The next day he vomited repeatedly, and was fretful and ill. A lumbar puncture, done by the house-physician on a suspicion of meningitis, yielded a clear fluid. When seen later that evening by one of us (R. C. M.) he was found to be restless and ill, with marked dehydration; but afebrile and not suffering from shock. His facial colour was good. He appeared to have abdominal pain and resented examination of the abdomen, but nothing abnormal was found there. Rectal examination was negative. The bowels had not been open for thirty-six hours. There was no evidence of intussusception. A diagnosis of acute high intestinal obstruction was made, but after consultation with a surgeon it was decided not to operate. In view of the child's dehydration, a ureteric catheter was tied into the saphenous vein at the ankle and a continuous intravenous drip infusion started, using Hartman's solution followed by 10 per cent. glucose solution. The child improved greatly in general condition and for twenty hours there was no further vomiting. After this interval, the vomiting started again and the question of a laparotomy was reconsidered, and the child was referred (on March 14) to one of us (A. S.) for a second surgical opinion. The child was obviously ill and still somewhat dehydrated. In the abdomen a mass was felt on the right side close to the umbilicus. This was elongated and sausage-shaped.

As the child was moved from the dorsal to the lateral position, the tumour swung on its transverse axis from a vertical to a transverse lie. An exact diagnosis as to the nature of the mass was not made, but a laparotomy was done for the acute obstruction.



FIG. 1.

At the operation, a mass was found blocking the jejunum about eighteen inches from the duodenal-jejunal flexure, the bowel above being grossly distended. The mass was removed from the jejunum, the latter was repaired and the abdomen closed. The intravenous drip was continued for some time after the operation.

The child managed to make a complete examination of his incision, with resultant sepsis, but apart from this his convalescence was uneventful and he was discharged a month after the operation, completely healed and in good health.

The illustration (fig. 1) shows the trichobezoar as it appeared on removal from the jejunum. The 'body' measures $2\frac{1}{2} \times 1\frac{1}{2} \times 1\frac{1}{4}$ inches, and has a 'tail' about 2 inches long at each end. It is surprising that it could pass through the pylorus of a child of this age.

The colour of the hair is black, which raises the question of its origin, unless fair hair becomes black under prolonged action of the digestive juices.

Discussion

The case is of interest partly for some unusual clinical features. The surgeon who first saw the case was unwilling to operate partly because he felt that no adequate cause for obstruction was apparent; and the temporary remission of symptoms appeared to confirm that he was right. It would seem worth while considering bezoar in obscure abdominal cases in children, as well as in adults. This case is reported because of the apparent rarity of a trichobezoar in a male child, and the even more unusual feature of its causing acute intestinal obstruction by lodging in the jejunum.

Thanks are due to Sir Frederick Menzies, Chief Medical Officer of the L.C.C., and to Dr. W. L. MacCormac, Medical Superintendent of St. James's Hospital, L.C.C., for permission to publish this case.

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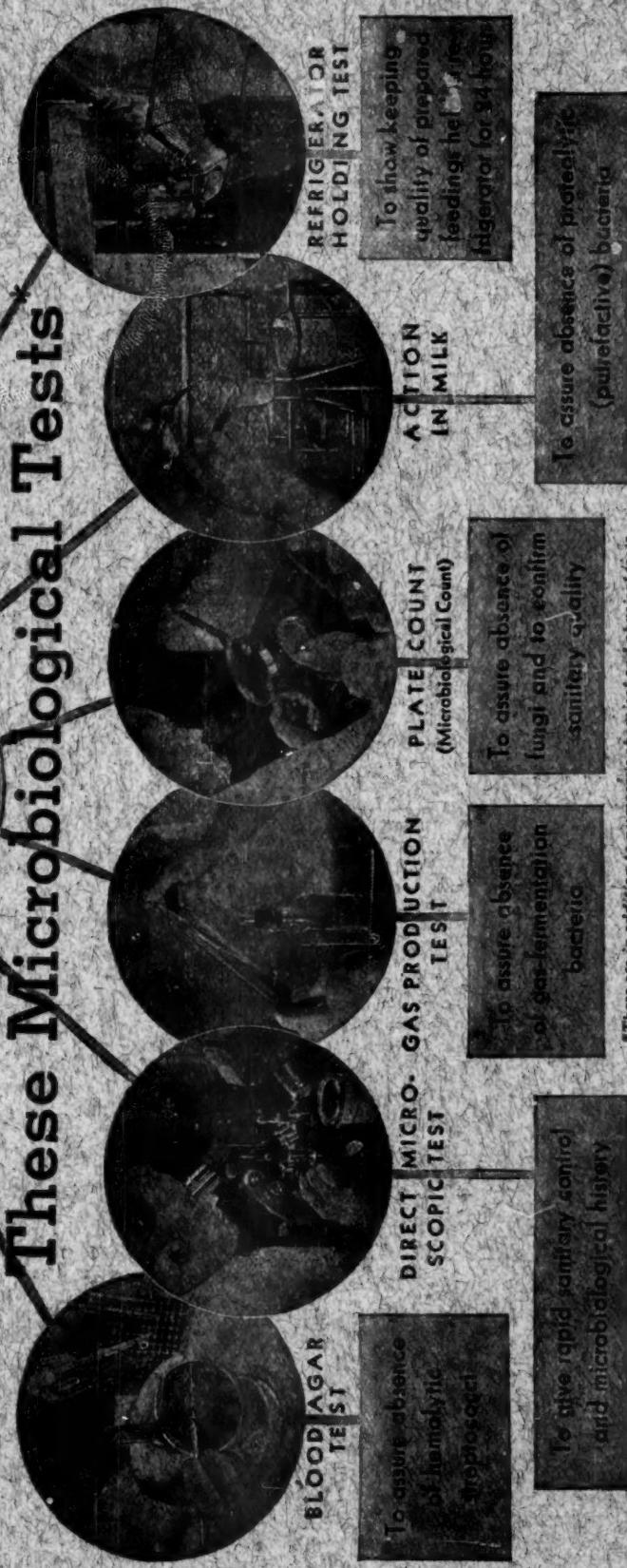
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